

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



LSHTM Research Online

van Zandvoort, Kevin; Checchi, Francesco; Diggle, Emma; Eggo, Rosalind M; Gadjroen, Kartini; Mulholland, Kim; McGowan, Catherine R; le Polain de Waroux, Olivier; Rao, V Bhargavi; Satzke, Catherine; +1 more... Flasche, Stefan; (2019) Pneumococcal conjugate vaccine use during humanitarian crises. *Vaccine*. ISSN 0264-410X DOI: <https://doi.org/10.1016/j.vaccine.2019.09.038>

Downloaded from: <http://researchonline.lshtm.ac.uk/4654483/>

DOI: <https://doi.org/10.1016/j.vaccine.2019.09.038>

**Usage Guidelines:**

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

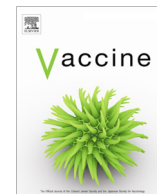
Available under license: <http://creativecommons.org/licenses/by/2.5/>

<https://researchonline.lshtm.ac.uk>



Contents lists available at ScienceDirect

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

## Review

## Pneumococcal conjugate vaccine use during humanitarian crises

Kevin van Zandvoort<sup>a,b,\*</sup>, Francesco Checchi<sup>a</sup>, Emma Diggle<sup>c</sup>, Rosalind M. Eggo<sup>a,b</sup>, Kartini Gadroen<sup>d,e</sup>, Kim Mulholland<sup>a,f</sup>, Catherine R. McGowan<sup>c,g</sup>, Olivier le Polain de Waroux<sup>a,b,h,j</sup>, V. Bhargavi Rao<sup>i</sup>, Catherine Satzke<sup>f</sup>, Stefan Flasche<sup>a,b</sup>

<sup>a</sup> Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

<sup>b</sup> Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK

<sup>c</sup> Save the Children UK, London, UK

<sup>d</sup> Médecins Sans Frontières, Amsterdam, the Netherlands

<sup>e</sup> Department of Medical Informatics, Erasmus MC, Rotterdam, the Netherlands

<sup>f</sup> Murdoch Children's Research Institute, University of Melbourne, Royal Children's Hospital, Melbourne, Victoria, Australia

<sup>g</sup> Department of Public Health, Environments, and Society, London School of Hygiene & Tropical Medicine, London, UK

<sup>h</sup> UK Public Health Rapid Support Team, London, UK

<sup>i</sup> Manson Unit, Médecins Sans Frontières (MSF UK), London, UK

<sup>j</sup> Public Health England, London, UK

## ARTICLE INFO

## Article history:

Received 16 May 2019

Received in revised form 16 August 2019

Accepted 9 September 2019

Available online xxxx

## Keywords:

Pneumococcal conjugate vaccine

Humanitarian crises

Humanitarian health

Refugees

Internally displaced people

Vaccination strategy

Pneumonia

## 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.

© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Contents

1. Introduction	00
2. <i>Streptococcus pneumoniae</i> in crises	00
3. Pneumococcal conjugate vaccines	00
4. Vaccination in crises	00
5. PCV use in crises	00
6. Evaluating optimal vaccination strategies	00
7. Conclusions	00
Contributors	00
Declaration of Competing Interest	00

\* Corresponding author at: Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, WC1E 7HT, London, United Kingdom.

E-mail address: [Kevin.Van-Zandvoort@lshtm.ac.uk](mailto:Kevin.Van-Zandvoort@lshtm.ac.uk) (K. van Zandvoort).

<https://doi.org/10.1016/j.vaccine.2019.09.038>

0264-410X/© 2019 The Authors. Published by Elsevier Ltd.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Please cite this article as: K. van Zandvoort, F. Checchi, E. Diggle et al., Pneumococcal conjugate vaccine use during humanitarian crises, Vaccine, <https://doi.org/10.1016/j.vaccine.2019.09.038>

Acknowledgements .....	00
References .....	00

## 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	+ <sup>i</sup>	+++	–	[25–27]
Low access to curative care	+ <sup>ii</sup>	+	+++	[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).

<sup>i</sup> Increase in carriage of vaccine-targeted serotypes, but not in overall carriage.

<sup>ii</sup> 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 disproportionately 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.

## Acknowledgements

KvZ, FC, CS and KM are supported by Elrha's Research for Health in Humanitarian Crises (R2HC) Programme, which aims to improve health outcomes by strengthening the evidence base for public health interventions in humanitarian crises. The R2HC programme is funded by the UK Government (DFID), the Wellcome Trust, and the UK National Institute for Health Research (NIHR).

SF was supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and Royal Society (grant number 208812/Z/17/Z).

RME acknowledges funding from an HDR UK Innovation Fellowship (grant MR/S003975/1).

CS is supported by an Australian NHMRC Career Development Fellowship (1087957) and a Veski Inspiring Women Fellowship. MCRI is supported by the Victorian Government's Operational Infrastructure Support Program.

The UK Public Health Rapid Support Team is funded by the National Institute for Health Research and the Department of Health and Social Care. The views expressed are those of the authors and not necessarily those of the NIHR or DHSC.

The funders had no involvement in the conceptualization, research, or writing of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

## References

- [1] United Nations High Commissioner for Refugees. Population statistics – Data – Demographics; 2018. <http://popstats.unhcr.org/en/demographics> [accessed July 29, 2019].
- [2] Sundberg R, Melander E. Introducing the UCDP georeferenced event dataset. *J Peace Res* 2013;50:523–32.
- [3] Croicu M, Sundberg R. UCDP GED codebook version 18.1; 2017.
- [4] Université catholique de Louvain CRED. EM-DAT: The emergency events database; 2019. <http://www.emdat.be>.
- [5] Toole M, Waldman R. The public health aspects of complex emergencies and refugee situations. *Annu Rev Public Health* 1997;18:283–312.
- [6] Heudtlass P, Speybroeck N, Guha-Sapir D. Excess mortality in refugees, internally displaced persons and resident populations in complex humanitarian emergencies (1998–2012) – insights from operational data. *Confl Health* 2016;10:15.
- [7] Thomas SL, Thomas SD. Displacement and health. *Br Med Bull* 2004;69:115–27.
- [8] Checchi F, Warsame A, Treacy-Wong V, Polonsky J, van Ommeren M, Prudhon C. Public health information in crisis-affected populations: a review of methods and their use for advocacy and action. *The Lancet* 2017;390:2297–313.
- [9] Checchi F, Gayer M, Grais RF, Mills EJ. Public health in crisis-affected populations: a practical guide for decision-makers. London: Humanitarian Practice Network, Overseas Development Institute; 2007.
- [10] Bellos A. Vaccination in humanitarian emergencies: literature review and case studies; 2012. [http://www.who.int/immunization/sage/meetings/2012/april/2\\_SAGE\\_WGVHE\\_SG1\\_Lit\\_Review\\_CaseStudies.pdf](http://www.who.int/immunization/sage/meetings/2012/april/2_SAGE_WGVHE_SG1_Lit_Review_CaseStudies.pdf) [accessed Nov 21, 2018].
- [11] Klugman KP, Dagan R, Malley R, Whitney CG. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. *Plotkin's vaccine*. Philadelphia: Elsevier; 2018.
- [12] Andrejko K, Hosangadi D, Cohen O, et al. WHO technical expert consultation report on optimization of PCV impact: review of evidence and programmatic considerations to inform policy; 2017.
- [13] Coldiron ME, Touré O, Frank T, Bouygues N, Grais RF. Outbreak of pneumococcal meningitis, Paoou Subprefecture, Central African Republic, 2016–2017. *Emerg Infect Dis* 2018;24:1720–2.
- [14] Crellen T, Rao VB, Piening T, Zeydner J, Siddiqui MR. Seasonal upsurge of pneumococcal meningitis in the Central African Republic. *Wellcome Open Res* 2018;3:134.
- [15] Bellos A, Mulholland K, O'Brien KL, Qazi SA, Gayer M, Checchi F. The burden of acute respiratory infections in crisis-affected populations: a systematic review. *Confl Health* 2010;4:3.
- [16] Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;18:1191–210.
- [17] Zivich PN, Grabenstein JD, Becker-Dreps SI, Weber DJ. Streptococcus pneumoniae outbreaks and implications for transmission and control: a systematic review. *Pneumonia* 2018;10:11.
- [18] Fonseca Lima E, Mello MJG, Albuquerque MFPM, et al. Risk factors for community-acquired pneumonia in children under five years of age in the post-pneumococcal conjugate vaccine era in Brazil: a case control study. *BMC Pediatr* 2016;16. <https://doi.org/10.1186/s12887-016-0695-6>.
- [19] Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. *Rev Infect Dis* 1990;12 (Suppl 8):S870–88.
- [20] Small C, Shaler CR, McCormick S, et al. Influenza infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. *J Immunol Baltim Md* 1950;2010(184):2048–56.
- [21] Zhou H, Haber M, Ray S, Farley MM, Panozzo CA, Klugman KP. Invasive pneumococcal pneumonia and respiratory virus co-infections. *Emerg Infect Dis* 2012;18:294–7.
- [22] Akramuzzaman SM, Cutts FT, Wheeler JG, Hossain MJ. Increased childhood morbidity after measles is short-term in urban Bangladesh. *Am J Epidemiol* 2000;151:723–35.
- [23] Dueger EL, Asturias EJ, Matheu J, Gordillo R, Torres O, Halsey N. Increasing penicillin and trimethoprim-sulfamethoxazole resistance in nasopharyngeal Streptococcus pneumoniae isolates from Guatemalan children, 2001–2006. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis* 2008;12:289–97.
- [24] Petrosillo N, Pantosti A, Bordini E, et al. Prevalence, determinants, and molecular epidemiology of streptococcus pneumoniae isolates colonizing the nasopharynx of healthy children in Rome. *Eur J Clin Microbiol Infect Dis* 2002;21:181–8.
- [25] Ojal J, Griffiths U, Hammit LL, et al. Sustaining pneumococcal vaccination after transitioning from Gavi support: a modelling and cost-effectiveness study in Kenya. *Lancet Glob Health* 2019;7:e644–54.
- [26] Choi YH, Jit M, Flasche S, Gay N, Miller E. Mathematical modelling long-term effects of replacing Prevnar7 with Prevnar13 on invasive pneumococcal diseases in England and Wales. *PLoS ONE* 2012;7:e39927.
- [27] Le Polain De Waroux O, Flasche S, Prieto-Merino D, Goldblatt D, Edmunds WJ. The efficacy and duration of protection of pneumococcal conjugate vaccines against nasopharyngeal carriage: a meta-regression model. *Pediatr Infect Dis J* 2015;34(8):858–64.
- [28] Singer M, Nambiar S, Valappil T, Higgins K, Gitterman S. Historical and regulatory perspectives on the treatment effect of antibacterial drugs for community-acquired pneumonia. *Clin Infect Dis* 2008;47:S216–24.
- [29] File TM, Schentag JJ. What can we learn from the time course of untreated and partially treated community-onset streptococcus pneumoniae pneumonia? A clinical perspective on superiority and noninferiority trial designs for mild community-acquired pneumonia. *Clin Infect Dis* 2008;47:S157–65.
- [30] Tedijanto C, Olesen SW, Grad YH, Lipsitch M. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. *Proc Natl Acad Sci* 2018;115:E11988–95.
- [31] Varon E, Levy C, De La Rocque F, et al. Impact of antimicrobial therapy on nasopharyngeal carriage of streptococcus pneumoniae, haemophilus influenzae, and branhamella catarrhalis in children with respiratory tract infections. *Clin Infect Dis* 2000;31:477–81.
- [32] Muthumbi E, Lowe BS, Muyodi C, Getambu E, Gleeson F, Scott JAG. Risk factors for community-acquired pneumonia among adults in Kenya: a case-control study. *Pneumonia Nathan Qld* 2017;9:17.
- [33] Dherani M, Pope D, Mascarenhas M, Smith KR, Weber M, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: a systematic review and meta-analysis. *Bull World Health Organ* 2008;86:390–398C.
- [34] Reisman J, Rudolph K, Bruden D, Hurlburt D, Bruce MG, Hennessy T. Risk factors for pneumococcal colonization of the nasopharynx in Alaska native adults and children. *J Pediatr Infect Dis Soc* 2014;3:104–11.
- [35] Collins DA, Hoskins A, Snelling T, et al. Predictors of pneumococcal carriage and the effect of the 13-valent pneumococcal conjugate vaccination in the Western Australian Aboriginal population. *Pneumonia* 2017;9. <https://doi.org/10.1186/s41479-017-0038-x>.
- [36] Stacey HL, Rosen J, Peterson JT, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults. *Hum Vaccines Immunother* 2019;15:530–9.
- [37] Trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults – full text view - ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03760146> [accessed July 31, 2019].
- [38] Grabenstein JD, Musher DM. Pneumococcal polysaccharide vaccines. *Plotkin's Vaccines*. Philadelphia: Elsevier; 2018.
- [39] Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. *PLoS Med* 2013;10:e1001517.
- [40] World Health Organization. Official country reported coverage estimates time series; 2018. [http://apps.who.int/immunization\\_monitoring/globalsummary/timeseries/tscveragebcg.html](http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscveragebcg.html) [accessed Feb 27, 2019].
- [41] Klugman KP. Herd protection induced by pneumococcal conjugate vaccine. *Lancet Glob Health* 2014;2:e365–6.
- [42] Loughlin AM, Hsu K, Silverio AL, Marchant CD, Pelton SI. Direct and indirect effects of PCV13 on nasopharyngeal carriage of PCV13 unique pneumococcal serotypes in Massachusetts' children. *Pediatr Infect Dis J* 2014;33:504–10.
- [43] Hammit LL, Akech DO, Morpeth SC, et al. Population effect of 10-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae in Kilifi, Kenya: findings from cross-sectional carriage studies. *Lancet Glob Health* 2014;2:e397–405.
- [44] Simonsen L, Taylor RJ, Young-Xu Y, Haber M, May L, Klugman KP. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *mBio* 2011;2(1).
- [45] World Health Organization. Global Routine Immunization Strategies and Practices (GRISP). World Health Organization; 2019 [accessed Feb 18, 2019] [http://www.who.int/immunization/programmes\\_systems/policies\\_strategies/GRISP/en/](http://www.who.int/immunization/programmes_systems/policies_strategies/GRISP/en/).
- [46] World Health Organization. Periodic intensification of routine immunization. World Health Organization; 2009 [accessed Feb 18, 2019] [https://www.who.int/immunization/programmes\\_systems/policies\\_strategies/piri\\_020909.pdf?ua=1&ua=1](https://www.who.int/immunization/programmes_systems/policies_strategies/piri_020909.pdf?ua=1&ua=1).
- [47] Ozawa S, Mirelman A, Stack ML, Walker DG, Levine OS. Cost-effectiveness and economic benefits of vaccines in low- and middle-income countries: a systematic review. *Vaccine* 2012;31:96–108.
- [48] Close RM, Pearson C, Cohn J. Vaccine-preventable disease and the underutilization of immunizations in complex humanitarian emergencies. *Vaccine* 2016;34:4649–55.
- [49] Nnadi C, Etsano A, Uba B, et al. Approaches to vaccination among populations in areas of conflict. *J Infect Dis* 2017;216:S368–72.
- [50] Lam E, McCarthy A, Brennan M. Vaccine-preventable diseases in humanitarian emergencies among refugee and internally-displaced populations. *Hum Vaccines Immunother* 2015;11:2627–36.

- [51] World Health Organization. Vaccination in acute humanitarian emergencies. A framework for decision making. World Health Organization; 2017.
- [52] Flasche S, Ojal J, Le Polain de Waroux O, et al. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. *BMC Med* 2017;15. <https://doi.org/10.1186/s12916-017-0882-9>.
- [53] Gargano LM, Hajjeh R, Cookson ST. Pneumonia prevention during a humanitarian emergency: cost-effectiveness of Haemophilus influenzae type B conjugate vaccine and pneumococcal conjugate vaccine in Somalia. *Prehospital Disaster Med* 2015;30:402–11.
- [54] Gargano LM, Hajjeh R, Cookson ST. Pneumonia prevention: Cost-effectiveness analyses of two vaccines among refugee children aged under two years, Haemophilus influenzae type b-containing and pneumococcal conjugate vaccines, during a humanitarian emergency, Yida camp, South Sudan. *Vaccine* 2017;35:435–42.
- [55] Unicef. Update on humanitarian mechanism; 2018. [https://www.unicef.org/supply/files/SESSION\\_7\\_2018\\_VIC\\_Update\\_on\\_Humanitarian\\_Mechanism.pdf](https://www.unicef.org/supply/files/SESSION_7_2018_VIC_Update_on_Humanitarian_Mechanism.pdf).
- [56] de Pereira A de L, Southgate R, Ahmed H, O'Connor P, Cramond V, Lenglet A. Infectious disease risk and vaccination in Northern Syria after 5 years of civil war: the MSF experience. *PLOS Curr Disasters* 2018. <https://doi.org/10.1371/currents.dis.bb5f22928e631dff9a80377309381feb> [published online Feb 2].
- [57] WHO[M14A: Vaccine purchase data. WHO. [http://www.who.int/immunization/programmes\\_systems/procurement/v3p/platform/module1/en/](http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module1/en/) [accessed July 31, 2019].
- [58] World Health Organization. The humanitarian mechanism. World Health Organization; 2017. [http://www.who.int/immunization/programmes\\_systems/sustainability/The\\_Humanitarian\\_Mechanism\\_ToRs.pdf?ua=1](http://www.who.int/immunization/programmes_systems/sustainability/The_Humanitarian_Mechanism_ToRs.pdf?ua=1).
- [59] Blanchet K, Ramesh A, Frison S, et al. Evidence on public health interventions in humanitarian crises. *The Lancet* 2017;390:2287–96.
- [60] Médecins Sans Frontières. Médecins Sans Frontières (MSF) briefing on provisional agenda item 20.1: Global vaccine action plan, Document A71/39; 2018. [https://msfaccess.org/sites/default/files/2018-05/WHO-WHA-71\\_MSF-briefing-GVAP-Agenda-Item-20-1.pdf](https://msfaccess.org/sites/default/files/2018-05/WHO-WHA-71_MSF-briefing-GVAP-Agenda-Item-20-1.pdf).
- [61] Ravelo JL. MSF bends donation policy for pneumonia vaccine. Devex; 2015 [accessed Feb 27, 2019] <https://www.devex.com/news/sponsored/msf-bends-donation-policy-for-pneumonia-vaccine-85317>.
- [62] Peyraud N, Quéré M, Duc G, et al. A post-conflict vaccination campaign, Central African Republic. *Bull World Health Organ* 2018;96:540–7.
- [63] Médecins Sans Frontières. Nigeria: 'There were hardly any children under 5 years of age'; 2016. <https://www.msf.ie/article/nigeria-there-were-hardly-any-children-under-5-years-age> [accessed Feb 27, 2019].
- [64] Médecins Sans Frontières. Vaccination activities in Médecins Sans Frontières; 2015. [https://www.who.int/immunization/sage/meetings/2015/october/MSF\\_SAGE\\_October2015\\_vf.pdf](https://www.who.int/immunization/sage/meetings/2015/october/MSF_SAGE_October2015_vf.pdf).
- [65] World Health Organization. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Wkly Epidemiol Rec* 2019;94:85–104.
- [66] Ager A, Burnham G, Checchi F, et al. Strengthening the evidence base for health programming in humanitarian crises. *Science* 2014;345:1290–2.
- [67] Heymann DL, Aylward RB. Mass vaccination: when and why. *Curr Top Microbiol Immunol* 2006;304:1–16.
- [68] Goldblatt D, Southern J, Andrews NJ, et al. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. *Lancet Infect Dis* 2018;18:171–9.
- [69] Temple B, Toan NT, Dai VTT, et al. Immunogenicity and reactogenicity of ten-valent versus 13-valent pneumococcal conjugate vaccines among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. *Lancet Infect Dis* 2019;19:497–509.
- [70] ClinicalTrials.gov. Identifier: NCT02943902, reduced PCV dosing schedules in South African Infants. ClinicalTrials.gov; 2016. <https://clinicaltrials.gov/ct2/show/NCT02943902> [published online Oct 25, accessed Feb 18, 2019].
- [71] Leaning J. Ethics of research in refugee populations. *The Lancet* 2001;357:1432–3.
- [72] Ojal J, Griffiths U, Hammit LL, et al. TSustaining pneumococcal vaccination after transitioning from Gavi support: a modelling and cost-effectiveness study in Kenya. *Lancet Glob Health* 2019;7:644–54.
- [73] Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Med* 2013;10:e1001527.
- [74] Flasche S, Jit M, Rodríguez-Barraguer I, et al. The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): a model comparison study. *PLOS Med* 2016;13:e1002181.
- [75] Le Polain De O, Waroux, Edmunds WJ, Takahashi K, et al. Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam. *Hum Vaccines Immunother* 2018;14:1939–47.
- [76] Havumaki J, Meza R, Phares CR, Date K, Eisenberg MC. Modeling cholera transmission and vaccination in a refugee camp. *Epidemiology* 2019. <https://doi.org/10.1101/514406>.
- [77] Finger F, Funk S, White K, Siddiqui MR, Edmunds WJ, Kucharski AJ. Real-time analysis of the diphtheria outbreak in forcibly displaced Myanmar nationals in Bangladesh. *BMC Med* 2019;17:58.
- [78] Finger F, Bertuzzo E, Luquero FJ, et al. The potential impact of case-area targeted interventions in response to cholera outbreaks: a modeling study. *PLoS Med* 2018;15:e1002509.
- [79] Kucharski AJ, Eggo RM, Watson CH, Camacho A, Funk S, Edmunds WJ. Effectiveness of ring vaccination as control strategy for Ebola virus disease. *Emerg Infect Dis* 2016;22:105–8.
- [80] Cooper BS, White LJ, Siddiqui R. Reactive and pre-emptive vaccination strategies to control hepatitis E infection in emergency and refugee settings: a modelling study. *PLoS Negl Trop Dis* 2018;12:e0006807.
- [81] Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008;5. <https://doi.org/10.1371/journal.pmed.0050074>.
- [82] Le Polain O, de Waroux, Cohuet S, Ndazima D, et al. Characteristics of human encounters and social mixing patterns relevant to infectious diseases spread by close contact: a survey in Southwest Uganda. *BMC Infect Dis* 2017;18. <https://doi.org/10.1101/121665>.
- [83] Althouse BM, Hammit LL, Grant L, et al. Identifying transmission routes of Streptococcus pneumoniae and sources of acquisitions in high transmission communities. *Epidemiol Infect* 2017;145:2750–8.
- [84] Weinberger DM, Pitzer VE, Regev-Yochay G, Givon-Lavi N, Dagan R. Association between the decline in pneumococcal disease in unimmunized adults and vaccine-derived protection against colonization in toddlers and preschool-aged children. *Am J Epidemiol* 2019;188:160–8.
- [85] Lopez Bernal JA, Andrews N, Amirthalingam G. The use of quasi-experimental designs for vaccine evaluation. *Clin Infect Dis* 2019;68:1769–76.
- [86] Silaba M, Ooko M, Bottomley C, et al. Effect of 10-valent pneumococcal conjugate vaccine on the incidence of radiologically-confirmed pneumonia and clinically-defined pneumonia in Kenyan children: an interrupted time-series analysis. *Lancet Glob Health* 2019;7:e337–46.
- [87] Bruhn CAW, Hetterich S, Schuck-Paim C, et al. Estimating the population-level impact of vaccines using synthetic controls. *Proc Natl Acad Sci U S A* 2017;114:1524–9.
- [88] UNHCR population statistics – Data – Demographics. <http://popstats.unhcr.org/en/demographics> [accessed July 29, 2019].