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UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Faculté de Médecine
Département de Médecine
Sociale et Préventive
Institut de Santé Globale

Thèse préparée sous la direction du Professeur Alain GERVAIX

Impact assessment of childhood immunization programs in limited-resource settings: challenges in ascertaining vaccination status and application to Pneumococcal Conjugate Vaccine in Burkina Faso

Thèse

présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur ès Sciences Biomédicales, mention Santé Globale

par

Lassané KABORE

Comité doctoral

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Prof. Annick Galetto-Lacour, membre

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1. List of scientific contributions

1.1. Contributions towards the doctoral dissertation

1.1.1. Articles published in peer-reviewed journals

1) **Lassané Kaboré**, Clément Z. Méda, François Sawadogo, Michèle M. Bengue, William MF. Kaboré, Alima T. Essoh, Alain Gervaix, Annick Galetto-Lacour, Isaïe Médah, Edouard Betsem. Quality and reliability of vaccination documentation in the routine childhood immunization program in Burkina Faso: Results from a cross-sectional survey. ***Vaccine*. 2020;38(13):2808-2815. doi:10.1016/j.vaccine.2020.02.023**
2) **Lassané Kaboré**, Seydou Ouattara, François Sawadogo, Alain Gervaix, Annick Galetto-Lacour, Robert Karama, Amado T. Traoré, Bertrand Méda, Haoua Tall, Alima T. Essoh, Bradford D. Gessner, Jennifer C. Moïsi. Impact of 13-valent pneumococcal conjugate vaccine on the incidence of hospitalizations for all-cause pneumonia among children aged less than 5 years in Burkina Faso: An interrupted time-series analysis. ***Int J Infect Dis*. 2020;96:31-38. doi:10.1016/j.ijid.2020.03.051**
3) **Lassané Kaboré**, Tolulope Adebanjo, Berthe Marie Njanpop-Lafourcade, Soumeya Ouangraoua, Felix T. Tarbangdo, Bertrand Méda, Srinivasan Velusamy, Brice Bicaba, Flavien Aké, Lesley McGee, Seydou Yaro, Edouard Betsem, Alain Gervaix, Bradford D. Gessner, Cynthia G. Whitney, Jennifer C Moïsi and Chris A.Van Beneden. Pneumococcal carriage in Burkina Faso after 13-valent pneumococcal conjugate vaccine introduction: results from two cross-sectional population-based surveys. ***The Journal of Infectious Diseases* 2021;224(S3): S258–66. doi: 10.1093/infdis/jiab037.**
4) **Lassané Kaboré**, Annick Galetto-Lacour, Annick Sidibé, Jennifer C. Moïsi, Alain Gervaix. Pneumococcal vaccine implementation in the African meningitis belt countries: The emerging need for alternative strategies. ***Expert Rev Vaccines*. 2021 Jun;20(6):679-689. doi: 10.1080/14760584.2021.1917391**

1.1.2. Oral communications

1) **Lassané Kaboré**, Seydou Ouattara, François Sawadogo, Alain Gervaix, Annick Galetto-Lacour, Robert Karama, Amado T. Traoré, Bertrand Méda, Haoua Tall, Alima T. Essoh, Bradford D. Gessner, Jennifer C. Moïsi. Impact of PCV13 on the incidence of hospitalizations for all-cause pneumonia among children aged less than 5 years in Burkina Faso: an interrupted time-series analysis. **International Symposium on the Pneumococcus and Pneumococcal Diseases (ISPPD), Toronto, 2020. Abstract accepted and published online, number 371. Section "Vaccines - Impact of Vaccine programs and Serotype Replacement". Available online: https://cslide.ctimeetingtech.com/isppd20/attendee/home**

1.2. Contributions not directly related to the doctoral dissertation

1.2.1. Articles published in peer-reviewed journals

1) **Kaboré L**, Yaméogo TM, Sombié I, et al. Plaidoyer pour un renforcement du système de pharmacovigilance au Burkina Faso. ***Santé Publique*. 2017;29(6):921-925. doi:10.3917/spub.176.0921.**
2) **Lassané Kaboré**, Bertand Meda, Isaie Médah, Stephanie Shendale, Laura Nic Lochlainn, Colin Sanderson, Ma Ouattara, William M F. Kaboré, Edouard Betsem, Ikechukwu U. Ogbuanu. Assessment of missed opportunities for vaccination (MOV) in Burkina Faso using the World Health Organization's revised MOV strategy: Findings and strategic considerations to improve routine childhood immunization. ***Vaccine*. 2020 Nov 10;38(48):7603-7611. doi:10.1016/j.vaccine. 2020.10.021.**

1.2.2. Manuscripts submitted to peer-reviewed journals and under review

1) Akinola Ayoola Fatiregun, Laura Nic Lochlainn, **Lassané Kaboré**, Modupeola Dosumu, Elvis Isere, Itse Olaoye, , Opeyemi Ekun, Samuel Agboola, Mojoyinola Ajila, Olaitan Suleiman, Rosemary Onyibe, Kofi Boateng, Richard Banda, Fiona Braka. Missed opportunities for vaccination among children visiting health facilities in a southwest State of Nigeria. ***PLoS One*. 2021 Aug 27;16(8):e0252798. doi: 10.1371/journal.pone.0252798.**

1.2.3. Manuscripts in preparation

1) **Lassané Kaboré**, Bertrand Meda, Berthe-Marie Njanpop-Lafourcade, Haoua Tall, Seydou Yaro, François Sawadogo et al. Effect of 13-valent pneumococcal conjugate vaccine dosing schedule on the nasopharyngeal carriage of *Streptococcus pneumoniae* among infants in Western Burkina Faso: Results from a randomized controlled open-label trial**.**

1.2.4. Oral communications

1) **L Kaboré**, F Sawadogo, B Njanpop-Lafourcade, T Ouro-Akpo. S Yaro, S Ouangraoua, SM Bagaya, ZC Meda, BD Gessner and JC Moïsi. Meningococcal and pneumococcal meningitis in Western Burkina Faso after the introduction of group A meningococcal conjugate vaccine (2010) and 13- valent pneumococcal conjugate vaccine (2013). **20th International Pathogenic Neisseria Conference (IPNC), Manchester, UK. September 2016 (Bill and Melinda Gates Scholarship Award).**

1.2.5. Master theses supervised

1) Facteurs associés à l'observance de la chimio prévention du paludisme saisonnier chez les enfants de 3 à 59 mois dans le district sanitaire de Tougan en 2016. Frederic Dianda's MPH thesis. Université de Ouagadougou, Burkina Faso. 2017.
2) Acceptabilité de la vaccination dans le District Sanitaire de Sig-Noghin, Ouagadougou. Augustin Zoungrana's MPH thesis. Université de Ouagadougou, Burkina Faso. 2018.

2. Abstract (English)

Background

Following the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in Burkina Faso in 2013, we undertook a series of studies aimed at documenting vaccine impact on pneumococcal carriage and disease. These studies included two cross-sectional pneumococcal carriage surveys (article 3), a hospital-based retrospective study on pneumonia-related hospitalizations among children aged < 5 years (article 2), and a literature review on the appropriateness of current PCV implementation strategies in the African meningitis belt (AMB) countries, including Burkina Faso (article 4). Essential to vaccine impact assessment are data on individuals' exposure to vaccination, which can only be verified in vaccination cards or in health facility registries. However, the reliability and the quality of these information sources are not well known. Thus, the other part of this doctoral research aimed at addressing this knowledge gap, through a cross-sectional survey (article 1).

Methods

Article 1

In 2016–17, a 6-week cross-sectional survey was conducted in 30 health facilities (HFs) selected from 10 health districts (HDs). Health workers and children aged < 24 months and their caregivers formed the study population. We evaluated the characteristics, completion patterns, and concordance of home-based (HBR) and facility-based records (FBR) to determine their reliability as data sources in estimating vaccine coverage. We computed proportions and concordance statistics and used logistic regression to explore predictors of information discordance.

Article 2

We retrospectively collected hospitalization data on children aged < 5 years in four rural district hospitals before and after PCV13 introduction, using available medical records. We estimated vaccine impact on the rates of pneumonia hospitalization, using a multivariable interrupted time-series model.

Article 3

Two population-based, cross-sectional, age-stratified surveys were conducted in 2015 and 2017 in the city of Bobo-Dioulasso. Standardized questionnaires were used to collect sociodemographic, epidemiologic, and vaccination data. Consenting eligible participants provided nasopharyngeal (all ages) and oropharyngeal (≥5 years only) swab specimens, which were plated onto blood agar either directly (2015) or after broth enrichment (2017). Pneumococcal isolates were serotyped by conventional multiplex PCR. Vaccine effect was evaluated by comparing the proportions of vaccine-type (VT) carriage among colonized individuals from a published baseline survey (2008) with each post-PCV survey, by age group.

Article 4

We retrieved from PubMed published studies on the epidemiology of the pneumococcus before the introduction of PCVs in the 26 countries of the AMB, and extracted or recalculated age distribution of cases and deaths, as well as the proportions of pneumococcal serotype 1. We also analyzed results from a few post-PCV studies to verify the presence of indirect effects,

with or without catch-up campaigns. A narrative synthesis was conducted to generate a hypothesis about the appropriateness of current PCV implementation strategies.

Selected results

The assessment of vaccination recording tools revealed that half (50.6%) of HBRs were non-standard and two-thirds (64.6%) of children were concerned with discordant information between HBRs and FBRs. Multivariate logistic regression model showed that standard HBR was protectively associated with discordant information (OR = 0.46, 95% CI: 0.26–0.81, p = 0.010).

The time-series analyses found a vaccine effectiveness of 34% (95% CI: 16–49%, p = 0.001), 24% (95% CI 2–41%, p = 0.032), and 50% (95% CI 30–64%, p < 0.001) against all-cause pneumonia among children <5 years, <2 years, and 2–4 years of age, respectively; this translated into an absolute reduction in the pneumonia hospitalization rate of 348 cases per 100, 000 person-years.

Carriage surveys recruited 992 (2015) and 1005 (2017) participants. Among pneumococcal carriers aged <1 year, VT carriage declined from 55.8% in 2008 to 36.9 % in 2017 (difference: 18.9%, 95% CI: 1.9%-35.9%, p=0.03); among carriers aged 1-4 years, VT carriage declined from 55.3% to 31.8% (difference: 23.5%, 95% CI: 6.8%-40.2%, p=0.004); among participants aged ≥ 5 years, no significant change was observed.

The review suggests that the current infant-only vaccination strategy will likely require more time to control pneumococcal disease at best, and that broader age mass vaccination campaigns might be the way forward.

Conclusion

We identified a range of issues around the recording of vaccination data, including the lack of standardization of recording forms, and inconsistent data recording practices. Short- and longer-term actions have been proposed to improve vaccination data quality. These shortcomings have implications on the design and analyzes of vaccine impact studies, such as resorting to ecological approaches which do not require individual vaccination data.

Data on pneumococcal carriage and disease indicate clear evidence of direct effects of PCV13 among vaccinated cohorts in Burkina Faso. However, there is still a lack of evidence of indirect effects of PCV among older children and adults who are not eligible for vaccination. Given the peculiarities of pneumococcal epidemiology in Burkina Faso and other AMB countries (the dominance of serotype 1 and the substantial lifetime risk of invasive pneumococcal infections), alternative PCV implementation strategies favoring direct vaccination of persons beyond early childhood need to be considered.

Keywords: Immunization; data recording; pneumococcal conjugate vaccine; impact; pneumonia; carriage; catch-up campaign; Burkina Faso.

3. Résumé (Abstract in French)

Contexte

À la suite de l'introduction du vaccin conjugué antipneumococcique 13-valent (PCV13) au Burkina Faso en 2013, nous avons entrepris une série d'études dans le but de documenter l'impact vaccinal sur la maladie à pneumocoque et le portage asymptomatique de ce germe.

Ces études comprenaient deux enquêtes transversales sur le portage (3ème article), une étude rétrospective hospitalière sur les hospitalisations pour pneumopathies chez les enfants de moins de cinq ans (2ème article), et une revue de littérature sur la pertinence des stratégies vaccinales actuelles avec le PCV dans les pays de la ceinture africaine de la méningite (CAM)(4ème article). Les données vaccinales individuelles sont essentielles pour les évaluations d'impact vaccinal, mais elles ont comme uniques sources les carnets ou les registres de vaccination des centres de santé. Or, la fiabilité et la qualité de ces sources d'information ne sont pas bien établies. De ce fait, l'autre partie de cette recherche doctorale a eu pour but de déterminer la fiabilité des différents modes d'enregistrements des vaccinations, à travers une enquête transversale (1er article).

Méthodes

1er article

En 2016-17, nous avons mené une enquête transversale de six semaines dans 30 centres de santé à travers 10 districts sanitaires. La population d'étude était constituée des agents de santé, des enfants de moins de 24 mois et leurs accompagnateurs. Nous avons évalué les caractéristiques, les modalités de remplissage, et la concordance des carnets et registres de vaccination afin de déterminer leur niveau de fiabilité. Nous avons calculé les proportions et les statistiques de concordance, et utilisé la régression logistique pour explorer les facteurs associés à la discordance d'information.

2ème article

Nous avons collecté rétrospectivement des données d'hospitalisation chez les enfants de moins de cinq ans dans quatre hôpitaux de district ruraux, en utilisant les enregistrements médicaux disponibles. Nous avons estimé l'impact vaccinal sur les taux d'hospitalisation pour pneumopathies, en utilisant un modèle multivarié de séries temporelles interrompues.

3ème article

Deux enquêtes populationnelles ont été menées en 2015 et 2017 dans la ville de Bobo-Dioulasso. Des questionnaires standardisés ont été utilisés pour la collecte de données sociodémographiques et épidémiologiques. Les participants éligibles et consentants ont fourni des écouvillonnages nasopharyngés (tout participant) ou oropharyngés (uniquement participants de ≥ 5 ans), qui ont ensuite été ensemencés sur gélose au sang soit directement (2015), soit après enrichissement au bouillon (2017).

Les souches de pneumocoque ont été sérotypées par la PCR conventionnelle multiplex. L'efficacité vaccinale a été évaluée en comparant les proportions de sérotypes vaccinaux parmi les sujets porteurs de pneumocoque dans une étude pré-vaccinale datant de 2008, avec celles des enquêtes post-vaccinales de 2015 et 2017, par tranche d'âge.

4ème article

Nous avons recherché dans PubMed des articles publiés sur l'épidémiologie du pneumocoque avant l'introduction du PCV dans les 26 pays de la CAM. Nous avons ensuite extrait ou recalculé la répartition des cas et décès par tranche d'âge et la proportion des cas dus au pneumocoque de sérotype 1. Nous avons aussi analysé les résultats de quelques études post-PCV afin de vérifier la présence d'effets indirects, avec ou sans campagne de rattrapage à l'introduction du vaccin. Une synthèse narrative a permis de générer une hypothèse concernant la pertinence des stratégies vaccinales actuelles.

Quelques résultats

L'évaluation des outils a montré que la moitié (50,6%) des carnets de vaccination n'étaient pas conformes au modèle standard, et que deux tiers (64,6%) des enfants étaient concernés par une discordance d'information. Avoir un carnet de vaccination à jour avec le programme de vaccination (ie conforme) était associé de manière protective à la survenue de discordance d'information vaccinale (OR = 0,46, IC 95%: 0,26–0,81, p = 0,010).

L'analyse des séries temporelles a trouvé une efficacité vaccinale de 34% (IC 95%: 16–49%, p = 0,001), 24% (IC 95%: 2–41%, p = 0,032), et 50% (IC 95%: 30–64%, p < 0,001) contre la pneumonie clinique parmi les enfants de moins de 5 ans, de moins de 2 ans, et de 2 à 4 ans, respectivement; ce qui se traduit par une réduction absolue des hospitalisations pour pneumonies de 348 cas pour 100, 000 personnes-années.

Pour l'enquête de portage, parmi les sujets porteurs du pneumocoque et âgés de moins d'un an, la proportion des sérotypes vaccinaux a baissé de 55,8% en 2008 à 36,9% en 2017 (différence: 18,9%, CI 95%: 1,9%-35,9%, p=0.03); parmi ceux âgés de 1 à 4 ans, elle a baissé de 55,3% à 31,8% (différence: 23,5%, IC 95%: 6,8%-40,2%, p=0,004); parmi les participants de plus de 5 ans, aucun changement significatif n'a été observé.

La revue concernant l'épidémiologie du pneumocoque suggère qu'au-delà des stratégies vaccinales en cours de mise en œuvre, des campagnes de vaccination de masse ciblant des tranches d'âge plus élargies pourraient être la voie à suivre.

Conclusion

Les insuffisances liées à l'enregistrement des données vaccinales comprennent entre autres le manque de standardisation et de mise à jour des outils, et des incohérences dans le remplissage de ces outils. Des actions à court et long termes ont été proposées pour améliorer la qualité des données. Ces insuffisances ont des implications sur la conception et l'analyse d'études d'impact vaccinal, comme le recours à des schémas écologiques qui ne nécessitent pas de données vaccinales individuelles. Les données sur le portage et la maladie à pneumocoque montrent clairement des effets directs du PCV13 parmi les enfants vaccinés. Cependant, il y a toujours une insuffisance de preuves quant aux effets indirects du vaccin chez les personnes non éligibles à la vaccination. Au regard les particularités de l'épidémiologie du pneumocoque au Burkina Faso et dans les autres pays de la CAM, des stratégies vaccinales alternatives, favorisant la vaccination directe de personnes au-delà de la petite enfance, devraient être examinées.

Mots-clés : Vaccination; enregistrement des données; vaccin conjugué antipneumococcique; impact; pneumonie; portage; campagne de vaccination; Burkina Faso.

4. Outline

5. List of abbreviations

AMB:	African Meningitis belt
AOM:	Acute otitis media
CAM	Ceinture africaine de la méningite
CDC:	Centers for Disease Control and Prevention (United States)
CFR:	Case fatality ratio
EIR	Electronic immunization registry
EPI	Expanded Program on Immunization
FBR:	Facility-based record
Gavi:	Global Alliance for Vaccines and Immunization
HBR:	Home-based records
HD:	Health district
HF:	Health facility
HIC:	High-income country
IPD:	Invasive pneumococcal disease
LMIC:	Low-and-middle-income country
lytA:	Autolysin gene
NP:	Nasopharyngeal
NVT:	Non vaccine type
OP:	Oropharyngeal
PCR:	Polymerase chain reaction
PPV23:	23 valent Pneumococcal Polysaccharide vaccine
PCV:	Pneumococcal Conjugate Vaccine
PCV7:	7 valent Pneumococcal Conjugate Vaccine
PCV10:	10 valent Pneumococcal Conjugate Vaccine
PCV13:	13 valent Pneumococcal Conjugate Vaccine
SAGE:	Strategic Advisory Group of Experts
STGG:	Skim milk, Tryptone, Glucose, and Glycerin
THY:	Todd Hewitt Yeast extract broth
VT:	Vaccine type
WHO:	World Health Organization

6. General introduction

6.1. The pneumococcus and pneumococcal disease

6.1.1. Biology and ecology of the pneumococcus

Streptococcus pneumoniae (also known as pneumococcus) is an extracellular Gram-positive encapsulated bacterium, discovered independently by Pasteur and Sternberg in 1881. The capsule of the pneumococcus, made of polysaccharides, is known for its important structural and serologic variability. It is a key virulence factor which confers to the bacterium protection against phagocytosis in the human host. Historically, the use of antisera to treat pneumococcal patients showed that immune protection was specific to the type of pneumococcus, and this led to the discovery of a large number of pneumococcal serotypes and serogroups. A serotype has been defined as pneumococcal strains producing polysaccharide with unique chemical structure and serologic immunologic properties, while a serogroup includes serotypes that have some common serologic properties with cross-reactive antibodies; for instance, serogroup 19 comprises serotypes 19A, 19B, and 19F [(1-4)].

S. pneumoniae colonizes the human nasopharynx, adhering to the epithelial cells thanks to the electrical properties of the capsule. While this cohabitation is often asymptomatic, the bacterium can sometimes spread to other surrounding organs such as the ears, the sinuses, and the lungs via the bronchi, causing a range of diseases including sinusitis, otitis, pneumonia, meningitis, and sepsis. The carriage rate of the pneumococcus in healthy persons can vary between 5% and 90%, but it tends to decrease with age and last longer in children [(2,3)]. Higher carriage rates have been documented in low- and middle-income countries (LMICs) and in indigenous populations of high-income countries (HIC)[(5)].

S. *pneumoniae* is transmitted horizontally from a carrier to individuals in the direct environment, mainly through respiratory droplets. Community spread of the bacterium is influenced by factors such as crowding, season, and ongoing upper respiratory tract infections[(3)].

6.1.2. Clinical manifestations of pneumococcal infections

S. pneumoniae is responsible for a range of diseases in humans, depending on the site infected. The literature distinguishes invasive pneumococcal diseases (IPD) from other pneumococcal infections. IPD refers to severe and invasive infections whereby the pneumococcus can be retrieved from otherwise sterile sites, such as the bloodstream. Examples of IPD include sepsis (clinical systemic manifestations of a severe infection), bacteremia, osteomyelitis, and meningitis. Non-IPD include milder and more common infections such as conjunctivitis, sinusitis, and acute otitis media (AOM). Another frequent illness is community-acquired pneumococcal pneumonia, which may be associated with bacteremia (15–30% of patients) or not. Pneumococcal pneumonia without bacteremia is classified as non-IPD[(6)].

Known risk factors for pneumonia in children include the lack of exclusive breastfeeding, nutritional deficiencies and indoor air pollution[(7)]. The proportion of pneumonia attributable to *S. pneumoniae* is not known precisely but has been estimated at around 30% by different

sources [3,5]. IPDs are associated with high case fatality rates (CFR), especially in children; in LMICs, the CFR for pneumococcal meningitis can be as high as 50% [5, 8-9].

Pneumococcal disease is mostly sporadic, but outbreaks may occur in closed institutions[5]. Moreover, large, serotype-1-dominated pneumococcal meningitis outbreaks have been reported from the African meningitis belt (AMB), including Burkina Faso[8] and Ghana [10,11]. Survivors of pneumococcal meningitis, particularly from Africa, are at high risk of developing long-term neurological sequelae, including motor abnormalities, hearing loss and mental retardation. The reported median prevalence of sequelae is 24.7%, with an interquartile range of 16.2-35.3% [12].

6.1.3. Public health and economic burden of pneumococcal disease

In 2000, before the widespread use of pneumococcal vaccines, *S. pneumoniae* caused 826, 000 deaths out of 14.5 million cases of serious pneumococcal disease in children aged 1-59 months worldwide, representing 11% of all deaths in this age group; in Africa, the number of cases and deaths was 4,060,000, and 447,000, respectively; in Burkina Faso, the mortality rate in the same age group was estimated between 300 and 500 deaths per 100, 000 children[13].

Previous studies based on surveillance data reported on the burden of pneumococcal meningitis in Burkina Faso. In the region of Bobo Dioulasso, Yaro et al [8] found over the period 2002-2005 an incidence of 14 cases per 100, 000 (33 per 100,000 in persons aged < 5 years) and a case fatality rate (CFR) of 46%; subsequently (2007-2009), Mueller et al [14] documented an incidence of 8.9 per 100,000 (15.9 per 100,000 among persons < 5 years); in a more recent pre-PCV national study (2011-2013), Kambiré et al found[15] a CFR of 23%, 30%, and 32%, overall, in infants < 1 year, and in adults aged ≥ 30 years, respectively.

A post-PCV global study reported a 51% reduction in pneumococcal mortality (from the level established in 2000) among children aged 1-5 years, in 2015; in absolute terms however, this still represented 294,000 lives loss, half of which occurred in India, Pakistan, Nigeria, and Democratic Republic of Congo [16].

The economic burden of pneumococcal disease has also been investigated extensively [17-21]. In Turkey for instance[21], the total (direct and indirect) median cost of pneumococcal meningitis in children <5 years was estimated at 4,068.30 Euros, including 80% of direct costs. In Ghana, the average cost of treating meningitis (unspecified etiology) was estimated at 101.7 USD per household; the number of working days loss by household members was estimated at 29 days per meningitis case[20].

6.2. Control measures for pneumococcal disease

6.2.1. Diagnosis

Although pneumococcal disease can be diagnosed clinically based on symptoms, signs or chest X-rays, a definitive diagnosis relies on laboratory technique to isolate or detect the organism from biological specimens such as cerebrospinal fluid and blood; however, in case of non-bacteriemic disease (some forms of pneumonia, acute otitis media), testing specimens may yield false negative results[5]. The following methods are available for pneumococcal detection and serotype characterization.

1) Pneumococcal identification

- Culture

S. pneumoniae can be cultured and identified based on specific characteristics. On a blood agar plate, the bacterium forms alpha-hemolytic colonies. The Gram staining reveals Gram-positive diplococci or Gram-positive cocci in short chains. The catalase test must be negative; if in addition, the growth is inhibited by optochin (ethyldocupreine hydrochloride) by at least a 14 mm diameter, *S. pneumoniae* is confirmed; if the colony is resistant to optochin (diameter <14 mm) but bile soluble, *S. pneumoniae* is confirmed. One advantage of the isolation by culture is the possibility of testing susceptibility to antibiotics. The main disadvantage is the relatively low sensitivity, which can be attributable to suboptimal storage and transportation conditions, the lack of mastery of the techniques, and prior use of antibiotics [22-24].

- Molecular methods

Polymerase chain reaction (PCR) can be used to detect bacterial DNA and thus confirm diagnosis. As it does not require live cells, this method is more sensitive than culture. Both real-time and conventional PCR techniques allow for the confirmation of *S. pneumoniae* through the detection of specific genes, including the autolysin gene (lytA). LytA PCR assays have been shown to best discriminate *S. pneumoniae* from other genotypically similar species in the same genus, such as *S. mitis*, *S. oralis*, and *S. pseudopneumoniae* [22,25-26].

- Antigen detection

Rapid diagnostic tests have been developed to detect the pneumococcus in adults with community acquired pneumonia. These tests are less specific in children. There is a lack of consensus for their use in routine practice [27,28].

2) Serotyping

When the presence of S. *pneumoniae* is confirmed, further methods can be used to determine the specific serotypes. These include Quellung reaction and multiplex conventional PCR.

- Quellung reaction

Quellung reaction (also known as Neufeld reaction) consists of putting specific antiserum (commercially available) in contact with pneumococcal polysaccharide. The binding forms an antigen-antibody reaction, leading to a change in the refractive index of the capsule which appears swollen and more visible. The addition of methylene blue creates contrasts, allowing for the detection of positive reaction using microscopy [22,23,29].

- Multiplex conventional PCR

The labor and costs associated with Quellung reactions led to the development of PCR assays to detect pneumococcal serotypes. Multiplex conventional PCR uses 9 reactions to detect up to 40 different serotypes, the list of which can be modified based on the most prevalent serotypes in specific settings [22,26].

6.2.2. Treatment

Pneumococcal infections can be treated with a range of antibiotics. Actual treatment modalities will depend on the site infected and local antimicrobial susceptibility profile. Ginsburg and colleagues[30] conducted a meta-analysis over three decades (1978-2011) to examine antimicrobial susceptibility of pneumococci isolated from community-acquired infections in Africa. They found a widespread non-susceptibility to trimethoprim-

sulfamethoxazole (64.5%); non-susceptibility rates to ampicillin and penicillin were 8.6 % and 19.3%, respectively; non-susceptibility to ceftriaxone/cefotaxime was 0.9%. In a small study on 15 adults diagnosed with community-acquired pneumococcal pneumonia in Mozambique, all pneumococci were susceptible to erythromycin, but 44% were resistant to trimethoprim-sulfamethoxazole[31]. In a 20-year (1997-2016) longitudinal surveillance project conducted in North America, Europe, Latin America, and the Asia-Pacific Region, authors analyzed the susceptibility profile of 6,566 pneumococcal isolates, the majority (77%) of which were from respiratory tract infections, and 25% from pediatric patients. Penicillin susceptibility varied between 70.7% in Europe to 52.4% in Asia over the entire study period. Susceptibility rates to amoxicillin-clavulanate, ceftriaxone, erythromycin, and vancomycin were 93.9%, 87.1%, 63.1%, and 100%, respectively. Multi-drug resistance (defined as non-susceptibility to at least three classes of antimicrobial agents) and extensively drug resistance (defined as non-susceptibility to at least five classes of antimicrobial agents) were observed in 20.1% and 4.4% of isolates, respectively [32]. They also observed an improvement of *S. pneumoniae* susceptibility to many antibiotics following the implementation of PCVs, possibly through a reduction in the circulation of the serotypes most prone to developing resistance[33].

6.2.3. Vaccination

1) Pneumococcal vaccines

Vaccination is a key strategy for the prevention and control of pneumococcal disease, including childhood pneumonia.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) was licensed in 1983 for use in the elderly and immunocompromised individuals. It contains only capsular polysaccharide of 23 different serotypes of the pneumococcus and induces T-cell-independent B cell response; this vaccine does not induce immunologic memory, nor does it elicit antibody response in children younger than 2 years. The 7-valent pneumococcal conjugate vaccine (PCV7) was licensed in 2000. It is made of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F polysaccharide capsular antigen conjugated to non-toxic diphtheria CRM197 protein. PCV7 involves a T-cell-dependent immunologic response and generate protective antibodies in infants and young children. It was introduced in routine immunization programs in high-income countries. In 2009, a 10-valent pneumococcal conjugate vaccine (PCV10) was licensed; it included serotypes 1, 4, 5, 6B, 7F, 9V, 14, 23F polysaccharide conjugated to non-typeable *Haemophilus influenzae* protein D, and serotypes 18C and 19F serotypes conjugated to tetanus and diphtheria toxoid. As a conjugate vaccine, PCV10 induces the production of protective antibodies in vaccinated infants. The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in 2010 and contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F polysaccharide capsular antigen conjugated to non-toxic diphtheria CRM197 protein; it is also immunogenic in infants [5,34].

The most recent vaccine to be licensed is another 10-valent pneumococcal conjugate vaccine (PCV10) containing serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19 A, 19F, and 23 F. Manufactured in India and prequalified by the World Health Organization (WHO), it is meant to be a cheaper alternative for low-income countries [35,36].

2) Recommended implementation strategies for PCVs

- PCV10 vs PCV13

Based on available data, the Strategic Advisory Group of Experts (SAGE) of the WHO[5] recommends both PCV10 and PCV13 for use in routine immunization programmes. The two products have comparable effects on disease caused by common serotypes, and evidence is lacking to conclude on the superiority of one product over the other regarding the overall impact on the burden of pneumococcal disease.

- Dosing schedule

The two dosing schedules recommended by the WHO are either 3 primary doses with no booster dose (3p+0), or 2 primary doses followed by a booster dose (2p+1). For the 3p+0 schedule, an interval of 4 weeks should be maintained between two consecutive doses; for the 2p+1 schedule, the 2 primary doses should be given at least 8 weeks apart, and the booster dose at 9-18 months[5]. The actual schedule choice should be based on programmatic considerations that can maximize coverage and timeliness. For instance, many countries which have adopted the 3+0 schedule align the 3 PCV doses with diphtheria-tetanus-pertussis (DTP)-containing vaccine doses to avoid the creation of additional contacts with the immunization programmes.

- Catch-up vaccination

When introducing PCV for routine use in infants aged < 1 year, it is recommended to conduct a catch-up vaccination campaign among children aged 1-5 years as a way to accelerate both direct and indirect effects of the programme. In resource-constrained settings, a narrower age group such as children aged < 2 years may be prioritized. One PCV dose may suffice for the catch-up vaccination of children aged ≥ 2 years, but for children aged 12-23 months, evidence is lacking to recommend the optimal number (one or two) of doses[5].

- Use of pneumococcal vaccines to respond to outbreaks

Pneumococcal meningitis outbreaks dominated by serotype 1 have been documented from the African meningitis belt [8,10-11], and PCV could be used to respond to future outbreaks. However, there is a limited evidence on the effectiveness of PCV in this context.

- Co-administration of pneumococcal conjugate vaccines with other vaccines

There are no established contraindications regarding the concomitant administration of PCV with other vaccines of routine immunization schedules such as DTP-containing vaccines, measles, and yellow fever vaccines.

3) Global trends on the use of pneumococcal conjugate vaccines

As of July 2020, 144 countries have introduced PCV in the routine childhood immunization schedule. Of these, 113 (78%) chose PCV13, 61(42%) a “3p+0” schedule, 58(40%) a “2+1” schedule, and 23(16%) a “3p+1” schedule. Up to 60 countries have introduced PCV with support from Gavi, including 51 (85%) choosing PCV13, and 52(87%) choosing a “3p+0” schedule [37].

Burkina Faso introduced PCV13 on October 31, 2013, using a “3p+0” schedule and without a catch-up campaign[38]. Since 2014, the coverage with 3 PCV doses has been higher than 90% [39].

6.3. Assessing the impact of pneumococcal conjugate vaccines

6.3.1. Rationale

The pneumococcus is one of the most important human pathogens considering the public health burden of pneumococcal disease. PCVs which have shown high efficacy levels in preventing pneumococcal disease during randomized controlled trials can be considered as a medical breakthrough, providing us with an important asset than can potentially help control pneumococcal disease. Yet, the pneumococcus remains a complex pathogen with more than 90 serotypes identified to date, several of which are known to consistently cause disease. Thus, current pneumococcal vaccines which cover only a limited subset of serotypes, may not be the panacea against pneumococcal disease; indeed, the outstanding serotypes could continue to cause disease. Furthermore, PCV are quite expensive products, and can have a significant impact on countries' public health budget. Hence the importance of monitoring the effects of these vaccines following their introduction in routine immunization programmes, not only to document overall impact on the morbidity and mortality of pneumococcal disease, but also to assess their cost-effectiveness vis-à-vis other competing interventions.

In high-income countries where PCV have first been implemented, pots-introduction studies have extensively documented significant reductions in the incidence of pneumococcal disease [40-45], even among unvaccinated segments of the population thanks to mounted herd immunity [43, 46-47]. However, in low-income countries where the advent of PCVs is more recent, whether and to which extent PCV will reduce pneumococcal disease can only be ascertained through post-introduction surveillance and special epidemiological studies. These studies are needed to generate context-specific knowledge on the following important questions.

1) Impact on pneumococcal disease and mortality

PCV impact on the following clinical outcomes can be assessed:

- Pneumonia

Much of the burden of pneumococcal disease is due to pneumonia, but etiological diagnosis of pneumonia is seldom done in routine clinical practice, making the assessment of the impact of PCVs on pneumonia challenging oftentimes. Nevertheless, clinically defined pneumonia could be used as a surrogate outcome to pneumococcal pneumonia, and thus to infer PCV impact [48,49].

- Pneumococcal meningitis and bacteremia

As these outcomes require laboratory confirmed diagnosis, it is possible to compare serotype-specific incidence between vaccinated and unvaccinated individuals. PCVs are mostly introduced nationwide simultaneously, which means countries may not have unvaccinated cohorts of the same age as vaccinated cohorts; in such situations, vaccine impact assessment is possible only using case-control studies[50], or before-after longitudinal surveillance[43, 51-54].

2) Impact on carriage

Herd immunity with PCV is achieved through elimination of asymptomatic carriage of the pneumococcus, which slows or stops its interpersonal transmission. Thus, monitoring the impact of PCV on carriage will provide data on their overall public health impact, including benefits among unvaccinated. Moreover, carriage studies can be implemented at discrete

time points before and/or after vaccine introduction, and therefore do not require high cost research infrastructure [55].

3) Impact on serotype distribution

By reducing the carriage of and disease due to serotypes included in PCVs, population vaccination may favor the emergence of other serotypes [43, 56-57]. This phenomenon known as serotype replacement may potentially offset the impact of vaccination programs if the emerging serotypes prove to be invasive. Thus, post-vaccine surveillance and studies should closely monitor the distribution of serotypes, and ideally compare it with pre-vaccine data.

6.3.2. Feasibility of vaccine-impact assessment in low-resource settings

Ideally, pneumococcal vaccine impact studies should include data on disease incidence before and after vaccine introduction, by serotype. This requires longitudinal surveillance facilities, including laboratory capacity to ascertain diagnosis, identify serotype and test susceptibility to antimicrobials. Equally important are reliable individual vaccination information and high-quality population data to derive denominators.

These resources are not readily available in most low-income countries. Exceptions in Africa include the Welcome-Trust-Kenya Medical Research Institute research platform in Kilifi, Kenya[58], and the UK MRC sites in the Gambia[59]. These sophisticated health and demographic surveillance sites have produced high-quality studies on disease burden and vaccine impact, among others.

Countries without such resources may be constrained in their capacity to assess the impact of new interventions such as vaccines. These limitations mean researchers must adapt study designs and overall approaches to obtain useful data[55]. For instance, carriage rates can be measured in a series of cross-sectional studies and used as surrogate estimates for vaccine effectiveness; ecological studies comparing periods or subnational geographies do not require individual-level comparisons.

6.4. Doctoral project justification and research questions

6.4.1. Context overview

Burkina Faso is a low-income, landlocked, Sahelian country situated in the middle of West Africa, with and area of 274,200 km^2 and an estimated population of 20.9 million in 2020. Nearly half of the population is younger than 15 years old; the fertility rate is 5.23 children per woman; life expectancy was 60 years for men and 61 for women in 2016; the annual birth cohort (children aged < 1 year) was 762,074 in 2017[60-62]. The under 5 mortality rate was estimated at 76 per 1000 live births [62], while 2017 maternal mortality rate was 320 per 100 000 live births [63]. HIV prevalence among adults aged 15-49 years old is 0.8%[64].

According to the World Bank [65]), 40% of the population live below the poverty line, and the country was ranked 144th (out of 157 countries) according to the new human capital index. Administratively, the country is subdivided into 13 regions, 45 provinces, 350 communes, and 8,228 villages[66]. Since 2016, the country is confronted with insecurity linked to terrorist attacks, leading to a humanitarian crisis with an increasing number of internally displaced persons[65].

The health system of Burkina Faso comprises an administration and an operational branch which provides health care.

The administration includes:

- central directorates and agencies centered around the Minister's cabinet.
- the intermediate level represented by 13 regional health directorates.
- the peripheral level represented by health districts (70 as of 2017).

The pyramidal public healthcare system comprises three levels:

- the first level made up of primary health facilities and district hospitals.
- the intermediate level, comprising regional hospitals.
- the third and upper level, comprises university teaching hospitals where tertiary care is provided[67].

Following the establishment of the Expanded Programme on Immunization (EPI) in 1974 [68], Burkina Faso began its implementation in 1980 [69]. Since then, the program continued to expand with the introduction of additional vaccines over years. Currently, the routine immunization schedule comprises 19 recommended vaccine doses, administered free of charge to children aged up to 18 months [70]. Vaccination data are manually recorded in vaccination cards (also called home-based records) and health facility registries. These recording forms are the main sources of individual vaccination information, particularly during vaccine coverage surveys.

Despites the lack country-specific laboratory confirmed data, the burden of pneumococcal disease in Burkina Faso is among the highest globally; in 2000, pneumococcal mortality was estimated between 300 and 500 deaths per 100, 000 children aged 1-59 months[13]. In 2014, more than 1.3 million ambulatory episodes of all-cause pneumonia were recorded in the country, 70% of which in children aged < 5 years[71]. Despites the microbiological diversity of the etiology of pneumonia, the pneumococcus is a major contributor to severe pneumonia, as supported by data from neighboring northern Togo[72].

Burkina Faso is among the few countries in Africa where pre-PCV studies have documented pneumococcal carriage and pneumococcal meningitis [8, 14-15], owing to collaborations that involved several partners such as the Ministry of Health, the Centre MURAZ of Bobo Dioulasso, the US Centers for Disease Control (US CDC), and the Agence de Médecine Préventive. These assets constitute an opportunity to undertake post-introduction studies to document PCV impact, and to provide decision-makers with relevant data to adjust vaccination strategies or justify renewed programmatic investments.

6.4.2. Knowledge gap and research questions

- Impact of PCV13 on pneumococcal carriage and disease

In the context of PCV13 introduction, the Ministry of Health of Burkina Faso in collaboration with US CDC engaged in a national pneumococcal meningitis surveillance project to document PCV impact. This work led to several publications which documented the incidence of pneumococcal meningitis before [15] and after PCV implementation [52,73].

To complement this work, data on the impact of PCV on carriage and pneumonia were needed. Thus, the Agence de Médecine Préventive set up a series of studies to close the knowledge gap on 1) PCV impact on carriage and 2) PCV impact on pediatric pneumonia.

As epidemiologist, study coordinator or principal investigator on these projects, it was agreed that we undertake PhD studies in Global Health at the University of Geneva, using the planned studies as dissertation topic; this was indeed viewed as an additional avenue to disseminate findings.

- Quality and reliability of the documentation of individual vaccination information

Besides disease status (diagnosis), any epidemiological study on vaccine impact in a given population also requires data on vaccination status, measured as a dichotomous (vaccinated/not vaccinated) or an ordinal variable (number of doses received). Hence, the critical importance of the quality of the recording of primary vaccination data following vaccine administration in health facilities. Anecdotal reports from our immunization-related

field work had indicated difficulties in ascertaining vaccination status of some children as a result of poor-recording practices or outdated vaccination cards. We therefore set out to conduct a formal assessment of the magnitude of this problem and to contribute to the limited literature of immunization records.

6.4.3. Goal and objectives

This doctoral work had the following goal and objectives:

1) Goal

To contribute to advance knowledge on:

- The quality and reliability of EPI vaccination data;
- The impact of PCV13 on pneumococcal carriage and disease.

2) Objectives

- To determine the reliability and quality of individual vaccination data and discuss implications for vaccine impact studies;
- To document the impact of PCV13 on asymptomatic carriage of the pneumococcus;
- To document the impact of PCV13 on all-cause pneumonia;
- To analyze PCV implementation strategy in Burkina Faso and other countries with comparable pneumococcal epidemiology.

6.4.4. Summary of the doctoral research project

The following table provides an overview of the different research questions, the proposed study design to address them, the research setting, and corresponding partnerships.

Table 01. Overview of the doctoral research project

Component	**Research question**	**Proposed design**	**Setting**	**Partners**
Reliability of individual vaccination information	To which extent can we rely on vaccination cards and registers to determine the vaccination status of a child in Burkina Faso?	Cross-sectional survey.	10 low-performing health districts in Burkina Faso.	- Agence de Médecine Préventive - Ministry of Health - Global Health Security Agenda project (US CDC)
Impact of PCV13 on asymptomatic carriage of the pneumococcus	What are the effects of PCV13 introduction on the asymptomatic carriage of the pneumococcus (both vaccine and non-vaccine serotypes) among vaccinated and unvaccinated age groups?	Cross-sectional surveys in 2015 and 2017, and comparisons with pre-PCV (2008) results.	Bobo Dioulasso (second largest city of the country).	- Agence de Médecine Préventive - Ministry of Health - Centre MURAZ - US CDC - Gavi
Impact of PCV13 on all-cause pneumonia	What are the effects of PCV13 on the rate of all-cause pneumonia related hospitalizations among children aged < 5 years?	Retrospective longitudinal study spanning 10 years (5 before and 5 after vaccine introduction), based on hospitalization records.	District's hospitals of Nouna (North-West), Orodara (West), and Séguénéga (North).	- Agence de Médecine Préventive - Ministry of Health - Pfizer Inc.
Appropriateness of current PCV implementation strategy in Burkina Faso and other comparable African countries	Is the current PCV implementation strategy appropriate for controlling pneumococcal disease?	Narrative literature review of the epidemiology of the pneumococcus and pneumococcal disease before and after PCV introduction.	The African Meningitis Belt (26 countries).	NA

PCV: Pneumococcal conjugate vaccine

6.4.5. Logic model

The following figure shows the logic model for the doctoral research project is shown is the following figure.

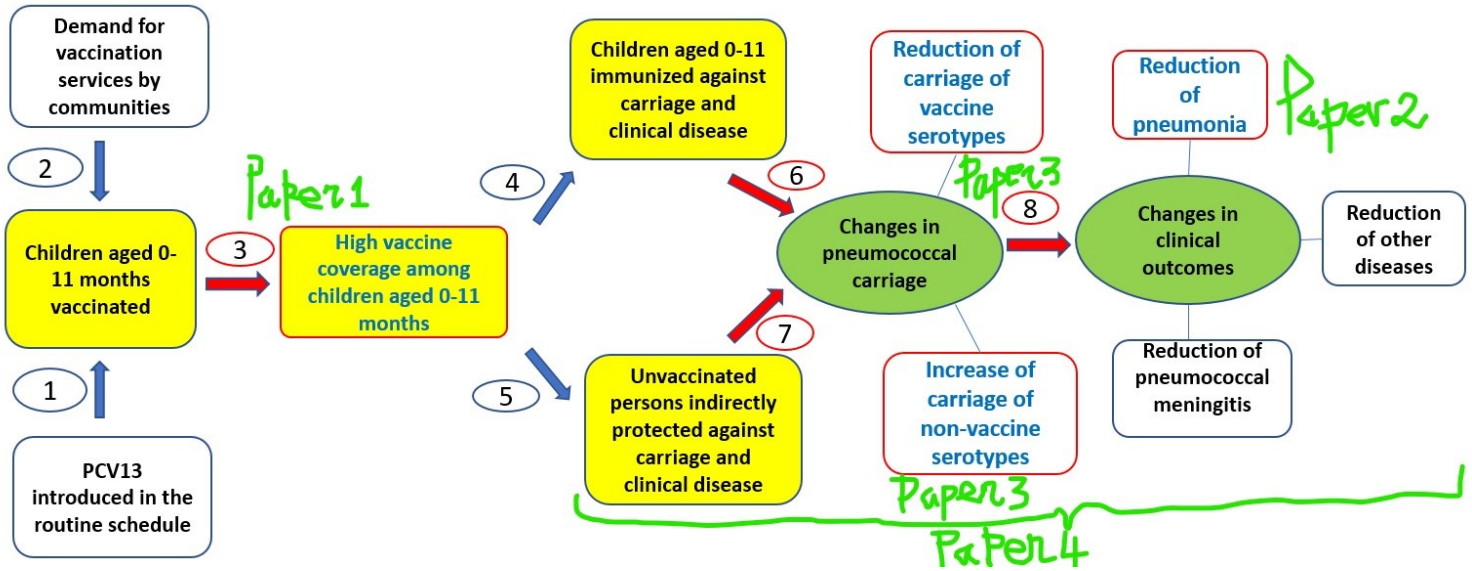

Figure 01. Logic model for the doctoral research project

Comment on the model:

- Vaccine introduction, followed by demand for vaccination services by communities will lead to children being vaccinated, resulting ultimately in high vaccine coverage among eligible children (aged 0-11 months).
- High vaccine coverage will yield direct protection for vaccinated individuals, and possibly indirect protection (herd immunity) for unvaccinated community members.
- Vaccine protection will lead to lower carriage of vaccine serotypes, and possibly to higher carriage of non-vaccine serotypes (serotype replacement)
- Finally, changes in carriage will be reflected by changes in clinical disease: as vaccine reduces carriage, it slows down the transmission rate, leading up to the reduction of clinical outcomes such as pneumonia, meningitis, and sepsis.

We aimed at verifying key relationships in the model, including 3, 6, 7, and 8.

7. Research articles

7.1. Methodological contributions of the PhD student to research articles

My contributions to the four articles that form the present dissertation are summarized in the following table.

Table 02. Methodological contributions to doctoral research work

Article	Role in project	Specific contributions				
		Protocol development	**Literature search**	**Data collection**	**Data analyses**	**Writing**
Quality and reliability of vaccination documentation	Epidemiologist and Field Coordinator	Wrote the first draft	Led literature search, appraisal, and synthesis.	Participated in the piloting of data collection tools. Supervised data collectors in the field.	Led data analyses with Stata, including descriptive statistics and logistic regression.	Developed the complete first draft and coordinated review by co-authors.
Impact of PCV13 on the incidence of hospitalizations for all-cause pneumonia among children < 5 years	Principal investigator	Wrote the first draft		Trained data collectors. Supervised a clinical research associate who monitored data accuracy and completeness in hospitals.	Led data analyses with Stata, including descriptive statistics and interrupted time-series analyses, using Poisson's regression to model counts and incidence rates.	
Impact of PCV13 on pneumococcal carriage	Epidemiologist and Field Coordinator	Wrote the first draft [a]		Trained and supervised data collectors. Contributed to the overall management of the survey.	Led data analyses with Stata, including descriptive statistics and comparisons between groups, accounting for clustering.	
Appropriateness of PCV implementation strategies in the African meningitis belt	Investigator [b]	Had the original idea and initiated the work		NA	Led the extraction of relevant epidemiological data from included studies.	

a: This paper presents pooled findings from two consecutive and complementary surveys conducted in 2015 and 2017; I had responsibilities for the 2015 survey which was led by the Agence de Médecine Préventive, but not for the 2017 one which was led by US Centers for Disease Control. b: This was a literature review and did not involve primary data collection. NA: Not applicable.

7.2. First article

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Quality and reliability of vaccination documentation in the routine childhood immunization program in Burkina Faso: Results from a cross-sectional survey

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Abstract

Introduction: Accurate and timely vaccination data are important to the Expanded Program on Immunization (EPI) to assess individual vaccination status and to monitor performance and vaccine coverage (VC). Since 2013, Burkina Faso introduced several new vaccines into the routine childhood immunization schedule. However, sustained efforts for a timely update and alignment of immunization home-based (HBRs) and health facility-based records (FBRs) with the evolving schedule were not implemented.

Methods: In 2016–17, we conducted a 6-week cross-sectional survey in 30 health facilities (HFs) across 10 health districts (HDs), targeting children aged < 24 months and their caregivers. Data collected included sociodemographics, availability of vaccination recording fields in HBRs, and vaccination dates. We evaluated the characteristics, completion patterns, and concordance of HBRs and FBRs to determine their reliability as data sources in estimating VC. A standard HBR was defined as one that had recording fields for all recommended 17 vaccine doses of the schedule, and discordance between HBR and FBR as having different vaccination dates recorded, or vaccination information missing in one of the records. We computed proportions and concordance statistics, and used logistic regression to explore predictors of discordance.

Results: We recruited 619 children, including 74% (n = 458) aged 0–11 months. Half (50.6%) of HBRs were non-standard. About two-thirds (64.6%) of children were concerned with discordant information. Compared to HBRs, FBRs were generally associated with low negative predictive values (median: 0.41; IQR: 0.16–0.70). Multivariate logistic regression model showed that standard HBR was protectively associated with discordant information (OR = 0.46, 95% CI: 0.26–0.81, p = 0.010).

Conclusion: We documented a lack of standardization of HBRs and frequent information discordance with FBRs. There is a pressing need to update and standardize vaccination recording tools and ensure their continuous availability in HFs to improve data quality in Burkina Faso.

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Abbreviations: BCG, Bacille Calmette et Guérin; EPI, Expanded Program on Immunization; FBR, Facility-based records; FIC, Fully immunized child; GHSA, Global Health Security Agenda; HBR, Home-base records; HD, health district; HF, Health facility; IPV, inactivated polio vaccine; MR, measles-rubella; NPV, Negative predictive value; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine; PPV, Positive predictive value; VC, vaccine coverage; WHO, World Health Organization.

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1. Introduction

Immunization is widely acknowledged as one of the most cost-effective and successful interventions in public health [1,2]. It is estimated that vaccines save as many as 2.5 million lives annually [3]. Following the 1974 World Health Assembly's recommendation to establish immunization and disease surveillance programs [4], Burkina Faso launched the standard Expanded Program on Immunization (EPI) in 1980 [5]. Since 2013, the program further expanded with the introduction of five new vaccines: rotaviru

and pneumococcal conjugate vaccines (PCV) in 2013; measles-rubella second dose in 2015; serogroup A meningococcal conjugate vaccine in 2017; and inactivated polio vaccine in 2018. Today, the national EPI schedule comprises 19 doses of vaccines recommended from birth to the age of 15–18 months [6].

Whilst this represents significant efforts towards reducing the burden of vaccine-preventable diseases, important challenges remain, including inadequate cold chain infrastructure [7] and poor data quality [8,9]. The introduction of new vaccines as observed in Burkina Faso should be an opportunity to revise and update vaccination recording forms [10], including FBRs and HBRs, to ensure proper data collection. Both can be valuable data sources in determining individual vaccination status for the purposes of service delivery and program performance review. However, recent evidence suggests these forms are often imperfect. Issues with FBRs include poor recording practices by immunization ser- vice providers, and failure to account for those who use services from different providers [11,12]; HBRs suffer from underutiliza- tion, lack of standardization in content, and stockouts [11,13–14]. Despites these limitations, the use of HBRs was recently recommended by World Health Organization (WHO), inasmuch as their positive health outcomes seem to outweigh the potential harm [15]. HBRs are increasingly the focus of field research, and previous reports have explored a range of aspects, including their characteristics [16,17], availability [13,16], and value in ascertaining individual vaccination status [17–19]. However, little is known about FBRs and HBRs as individual vaccination data recording tools in low-income settings with a relatively fast pace new vaccine introduction. In the absence of periodical, timely, and nationwide updates of these tools, capturing the exact vaccination picture of a given population could pose challenges [20]. Indeed, the administrative coverage (number of administered doses divided by the target population) used in routine performance reports is prone to numerator or denominator biases [9,21–23].

1. Methods

1.1. Study design and setting

The current work assessed the characteristics of HBRs and FBRs, their completion by vaccination providers, and their usefulness in estimating vaccine coverage (VC) in 10 health districts (HD) in Burkina Faso.

This was a cross-sectional paper-based questionnaire survey conducted between December 2016 and February 2017 in 10 out of the 70 HDs in Burkina Faso (Boulmiougou, Gaoua, Garango, Gourcy, Kaya, Koudougou, Pô, Kombissiri, Koupèla, and Ziniaré). These districts were targeted by a tripartite initiative (Ministry of Health, Agence de Médecine Préventive, and the United States Cen- ters for Disease Control and Prevention) in the context of the Glo- bal Health Security Agenda (GHSA) because they had the highest absolute numbers of children unvaccinated with the first dose of measles vaccine in 2015. This work was part of the immunization improvement component of this ongoing GHSA initiative [24].

Within each district, 3 HFs were selected to participate in the survey based on a convenience sampling and after consultation with district management teams. Selection criteria included the size of the population in the catchment area and geographical accessibility.

1.2. Selection of study participants

In each HF, we interviewed caregivers of children aged 0 to 23 months as they were exiting. A minimal sample of 20 partici- pants per HF was defined *a priori* (at least 600 for the 30 HFs) and stratified to include 15 caregivers of children aged 0 to 11 months and five caregivers of children aged 12–23 months. On the day of the survey, participants in each age group were consecutively enrolled until these predefined numbers were achieved. Having a HBR was required for inclusion.

1.3. Data collection

A structured questionnaire was used for data collection. Data collected included sociodemographic characteristics of the child and the caregiver; characteristics of the HBR such as the number and names of vaccine doses displayed; vaccination dates for all EPI vaccines received through the date of the survey according to the HBR and the FBR; and history of vaccination for all three doses of pneumococcal and rotavirus vaccines according to the caregiver. Information recall was limited to these vaccines because given simultaneously with pentavalent vaccine as an additional shot in the opposite thigh, and drinkable liquid in a single vial for PCV and rotavirus vaccine, respectively. We hypothesized that it was likely easier for caregivers to remember them as it was recently suggested that visual cues could improve vaccination recall [12].

Questionnaires also included HFs' characteristics such as the number of staff in charge of immunization, the availability of job description, experience of the EPI officer, and the availability and completion of immunization registers.

Due to logistical constraints, we could not use electronic devices for data collection, including pictures of all studied HBRs, as recommended in the WHO's vaccination coverage survey reference manual [25]. Consequently, only sample pictures were taken to illustrate the main types of HBRs encountered in the field.

Field work was conducted by experienced health professionals following training. The initial version of the questionnaire was field-tested in two HFs in a HD unrelated to the survey.

1.4. Data analyses

1.4.1. Operational definitions

- Standard vaccination HBR

The 17 vaccine doses recommended between birth and the age of 15–18 months in the national EPI schedule at the time of the study were Bacille Calmette et Guérin (BCG) and oral poliomyelitis vaccine (OPV) at birth; the 8, 12 and 16 weeks doses for i) OPV, ii) pentavalent (diphteria, tetanus, whole cell pertussis, hepatitis B and *Haemophilus influenzae* type b), iii) 13-valent pneumococcal conjugate vaccine (PCV13), and iv) rotavirus; yellow fever (YF) at 9–11 months and measles-rubella first (MR1) and second (MR2) doses at 9–11 months and 15–18 months, respectively. A standard HBR is one showing preprinted recording fields for all the above 17 items.

- Standard vaccination FBR

This was defined as the official and updated vaccination register supplied by the EPI directorate of the Ministry of Health.

- Fully immunized children

Fully immunized children (FIC) are those who received all recommended vaccines between their birth and the age of 12 months, that is, one BCG dose, four OPV doses (birth, 8, 12 and 16 weeks), three pentavalent doses (8, 12 and 16 weeks), three rotavirus doses (8, 12 and 16 weeks), three PCV doses (8, 12 and 16 weeks), one MR dose (9–11 months), and one YF dose (9–11 months) [8]. At the time of the survey, there was a national stockout for YF vaccine

due to global shortage [26]. We therefore accounted for this in the determination of the proportions of FIC.

- Discordance of vaccination information

Discordance between HBR and FBR was defined as having different vaccination dates recorded for at least one vaccine dose, or vaccination information missing in one of the records. The number of discordances for each child could then vary between 0 and 17.

1.1.1. Statistical analyses

After a single entry, data were checked and cleaned by a data manager. Descriptive statistics such as absolute and relative frequencies were generated. In addition, we considered discordance as an indicator of the quality of information recording by vaccina- tors and used simple regression to assess its associations with selected independent variables; thereafter, only variables with a p-value lower than 0.1 were entered into a multivariable logistic regression model.

We calculated dose-specific coverage for each of the 17 doses ofthe EPI schedule as well as the proportion of FICs using HBRs, FBRs, and a combination of both, respectively; denominators were all children age-eligible for each vaccine.

Sensitivity analyses for FICs also considered history of vaccination for all rotavirus and PCV doses (while keeping written evi- dence of vaccination for all other vaccine doses); children who received these vaccines according to their caregiver were consid- ered vaccinated even in the absence of written evidence.

The agreement between HBRs and FBRs was assessed by using the former as reference to calculate sensitivity, specificity, predic- tive values, concordance, and the Kappa statistic. A Kappa lower than 0.20 meant slight to poor agreement; 0.21–40, fair agree- ment; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [17].

The clustering of participants within HFs was taken into account through Stata *svyset* command [27], but analyses were unweighted because we could not calculate the probability of inclusion of each participant. All analyses were done in Stata (ver- sion 15, Stata Corporation, College Station, Texas).

P-values lower than 0.05 were considered statistically significant.

1.2. Ethical considerations

The current programmatic evaluation was approved by the Ministry of Health of Burkina Faso and conducted in close collaboration with EPI directorate. Although this was deemed to be a non-research activity, all respondents were asked to give their verbal consent before interviews. The final database (kept in a server with restricted access) does not contain any identifying information.

2. Results

2.1. Sociodemographic characteristics of participants

We enrolled a total of 619 children, including 458 (74.0%) aged 0–11 months, 302 (48.8%) females, and 352 (43.1%) from rural areas.

The number of children by HD varied between 60 (Garango) and 66 (Pô). The mother was the caregiver for 98% of the children; 53.3% of caregivers had no formal education.

2.2. Characteristics of health facilities

All 30 HFs were public. The number of staff in charge of immunization activities ranged from 1 to 10 with a median of 3. A job description was available in 17 HFs. Experience in managing EPI ranged from 0 to 25 years, with a mean of 6.3 years (standard deviation: 7.4). All HFs had registers to record vaccination data. Two thirds (20/30) of these FBRs were standard. The other third consisted of a variety of adaptations from the stan- dard version, and included three notebooks and seven locally- made FBRs.

2.3. Types and characteristics of home-based records

There was an important variation of the type of HBR (Fig. 1). Fig. 1a (standard version) was the most frequent type (n = 311), followed by Fig. 1c (n = 185). In the districts of Garango, Pô, and Ziniaré, HBRs without any pre-printed item for recommended EPI vaccines were encountered (n = 13); sheets of notebooks (Fig. 1b) and non-vaccination HBRs (Fig. 1d) were used to capture immunization data).

The median number of vaccine doses displayed on HBRs was 17 but varied between 10 for Boulmiougou and Gaoua HDs, and 17 for the other eight HDs (STable 1).

Of 615 HBRs assessed (information missing for 4 participants), 311 (50.6%) were considered standard. This proportion varied between 12.1% in Pô HD and 80.7% in Kaya HD (Fig. 2). Compared to urban areas, rural areas had a lower percentage of standard HBRs (44.3% vs 58.1%, p = 0.001). Similarly, children whose care- givers received no formal education had a lower percentage of standard HBRs compared to those whose caregivers received at least primary education (47.5% vs 55.7%, p = 0.05).

The proportions of HBRs that did not have dose-specific data recording field varied between 2.1% for BCG and 47.6% for MR2 (Fig. 3)

2.4. Completion of immunization facility and home-based records by vaccinators

Five immunization registers out of 30 (16.7%) were not fully updated with records on the most recent vaccination activities.

To assess the extent of under-recording of vaccinations on HBRs, we calculated the proportions of HBRs that had a recording field for rotavirus and pneumococcal vaccines among children who were unvaccinated according to the HBR, but vaccinated according to the FBR. At least 80% of HBRs did not have a recording field for each of the six vaccine doses (SFig.1), indicating that under-reporting occurs primarily when the HBR is outdated.

The completion of HBRs during vaccination was the responsibility of the vaccinator, another designated team member, or both in respectively eight (26.7%), 15 (50.0%), and seven (23.3%) HFs.

2.5. Comparison of vaccination information between HBRs and FBRs

- Agreement and discordance between HBRs and FBRs

The Kappa statistic for agreement between HBRs and FBRs varied between 0.005 and 0.74, with a median of 0.48 (IQR: 0.26–0.66) (STable 2). Compared to HBRs, FBRs were generally associated with low negative predictive values, with a median of 0.41 (IQR: 0.16–0.70).

Overall, 64.6% of children had discordant vaccination information between the HBR and the FBR. (Fig. 4). The frequency of discordance by vaccine-dose varied between 15.1% for BCG and 38.2% for MR2 (SFig. 2).

- Factors associated with information discordance between HBRs and FBRs

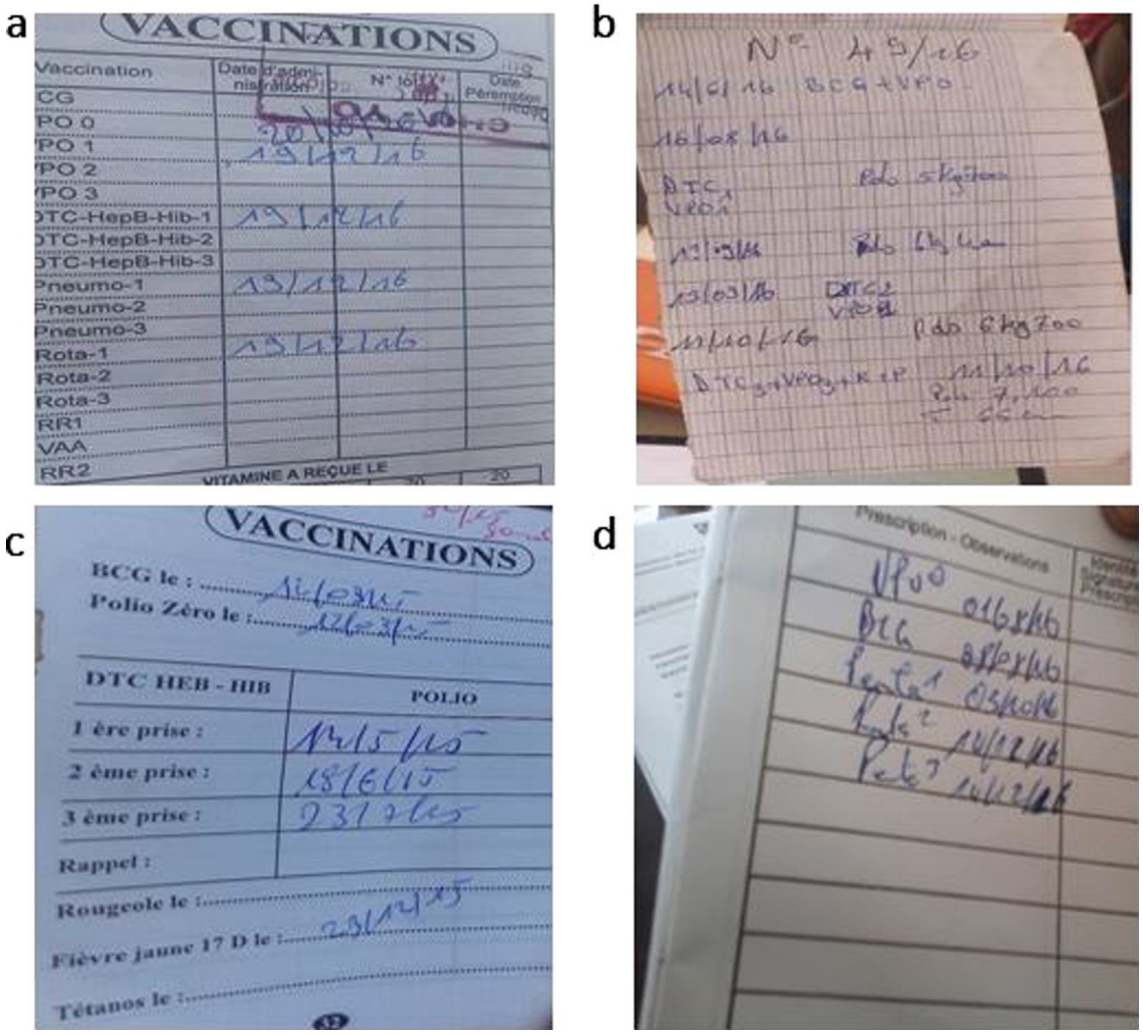


Fig. 1. Samples of the main types of home-based records, Burkina Faso, 2017. (a) Standard home-based record displaying all the 17 required items. (b) School note-book sheet used as home-based record. (c) Home-based record not displaying recently introduced vaccines (Rotavirus, PCV13 and measles-rubella second dose). (d) Curative consultation card used as vaccination home-based record (no vaccine item pre-printed).

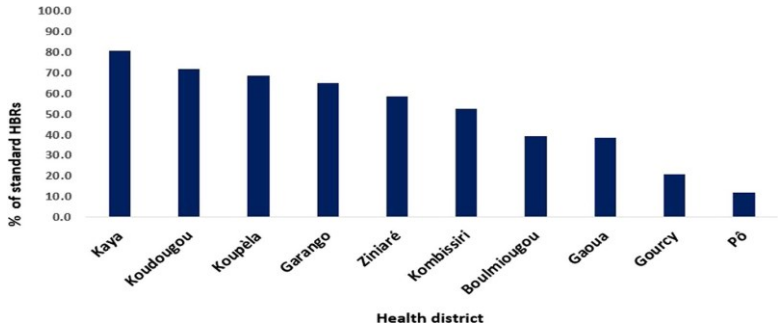


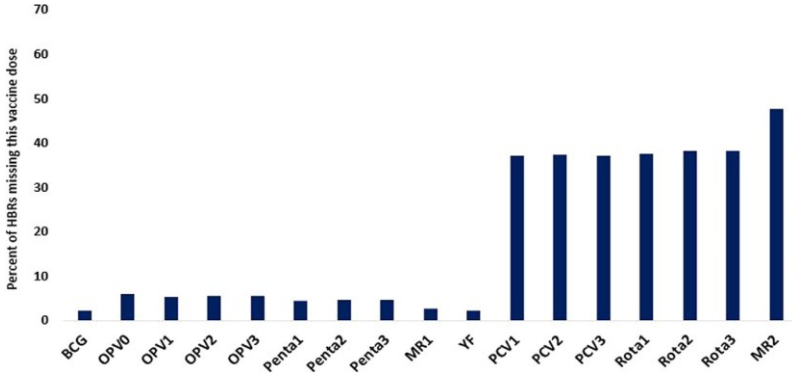
Fig. 2. Proportions of standard home-based records (HBRs) by health district, Burkina Faso, 2017.

Unadjusted analyses showed that age group, standard HBR, standard FBR, and timely completion of FBRs were significantly associated with discordance. In the multivariable logistic regression model, only being in the 12-23 months age group (OR = 3.05, 95% CI: 1.76–5.30, p = 0.000) and possessing a standard HBR (OR = 0.46, 95% CI: 0.26–0.81, p = 0.010) remained associated with discordance Table 1.

We also found a significant negative linear correlation (coefficient: ~~0.~~17, 95% CI: ~~0.3~~1; 0.~~02~~, p = 0.025) between the pres- ence of a preprinted recording field for a given vaccine dose on HBRs and the occurrence of HBR-FBR discordance on that vaccine-dose (SFig. 3).

- Antigen-specific coverage assessed by HBRs vs FBRs

Fig. 3. Proportions of home-based records (HBRs) that did not have dose-specific data recording field, Burkina Faso, 2017. BCG : Bacille Calmette et Guérin ; OPV : oral polio vaccine ; Penta : tetanus, whole cell pertussis, hepatitis B and Haemophilus influenzae type b ; Rota: rotavirus vaccine; PCV: pneumococcal conjugate vaccine; MR: measles- rubella; YF: yellow fever. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



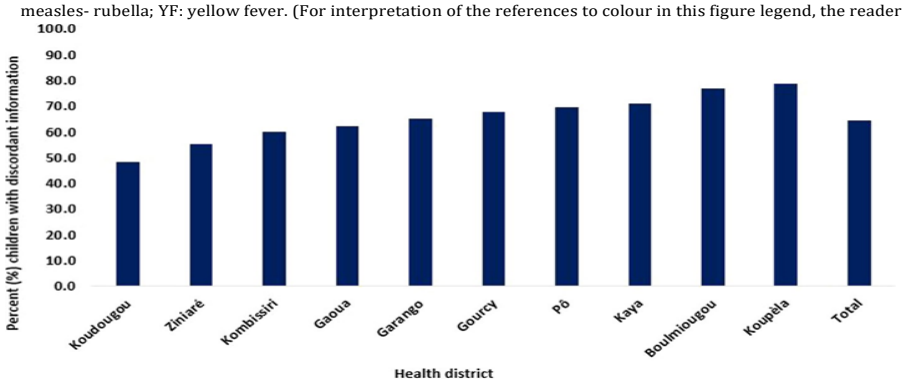


Fig. 4. Proportions of children with discordant vaccination information for at least one vaccine dose, Burkina Faso, 2017.

For all 17 vaccine doses, VC estimated with HBRs was greater than that with FBRs (Fig. 5).

- Fully immunized children assessed by HBRs, FBRS, and recall The

percentage of FICs were 42.9%, 32.7%, 45.3% and 64.9% for HBRs, FBRs, HBRs combined with FBRs, and HBRs combined with FBRs and recall, respectively. If YF vaccine was excluded, these percentages increased to 66.3.6%, 53.8%, 68.9% and 86.9%, respectively (Fig. 6).

3. Discussion

Analyzing data collected on HBRs and FBRs from 30 immunization facilities in Burkina Faso, we found that half of HBRs and a third of FBRs were outdated and unfit to properly capture individ- ual vaccination information. Higher proportions of outdated HBRs were found among rural children and those of uneducated care- givers. We also observed inconsistent completion of these forms, as one in six FBRs was not filled in with the latest vaccination infor- mation, and many vaccine doses, particularly those frequently lacking preprinted data recording fields in HBRs, were not recorded following vaccine administration. Agreement between HBRs and FBRs varied across vaccine doses, with a median of 0.48 (moderate agreement). Nearly two thirds of children were concerned with a discordance of vaccination information between HBRs and FBRs on at least one vaccine dose. Adding information obtained from caregivers' recall increased VC estimates.

Previous studies have assessed the characteristics of HBRs as routine immunization data recording tools. A recent assessment in Benin found that circulating HBRs needed to be updated to include serogroup A meningococcal conjugate vaccine, hepatitis B birth dose and rotavirus vaccines [28]. Similarly, a Kenyan study found that 6% of HBRs had no information on vaccination history [16]. In Lebanon, however, Mansour et al. found that all HBRs were displaying the name of each recommended vaccine per the national immunization schedule [17]. The diversity and lack of standardization of HBRs observed in our assessment was also reported in Vietnam [29].

One of the functions of HBRs is to ensure the continuity and coordination of care, including immunization, across health workers [11]. Given that outdated HBRs were more prevalent among rural and uneducated caregivers, this could result in an inequitable access to immunization services, and poorer health outcomes. Yet, equity is a current priority in the global immunization agenda [3,30].

Vaccine doses that are missing from HBRs were more likely to be under-recorded after their administration by vaccinators, which

Table 1
Associations between selected independent variables and discordance of vaccination information between home-based records and facility-based records, Burkina Faso, 2017.

Simple logistic regressions Independent variables	% of discordance	Oddsratio	95% CI	p
Age group 0– 11 months	59.3	Ref.		
12–23 months	83.2	3.40	2.01–5.75	<0,001*
Standard HBR No	74.7	Ref.		
Yes	56.5	0.44	0.24–0.79	0.008*
Standard FBR No	75.1	Ref.		
Yes	62.2	0.55	0.30–0.98	0.049*
Job description available No	71.1	Ref		
Yes	62.5	0.67	0.34–1.32	0.236
Number of health workers in charge of immunization <3	69.0	Ref		
>=3	63.9	0.80	0.44–1.43	0.42
Experience of the health facility EPI manager < 1 year	70.1	Ref		
>= 1 year	63.8	0.75	0.42–1.35	0.315
Completion of FBR Delayed	82.3	Ref		
Timely	62.9	0.36	0.14–0.91	0.032*
Multiple logistic regression **Independent variables**		**Odds ratio**	**95% CI**	**P**
Age group 0– 11 months		Ref.		
12–23 months		3.05	1.76–5.30	<0.001*
Standard HBR No		Ref.		
Yes		0.46	0.26–0.81	0.010*
Standard FBR No		Ref.		
Yes		0.68	0.33–1.41	0.288
Completion of FBR Delayed		Ref		
Timely		0.39	0.14–1.09	0.070

* Statistically significant.

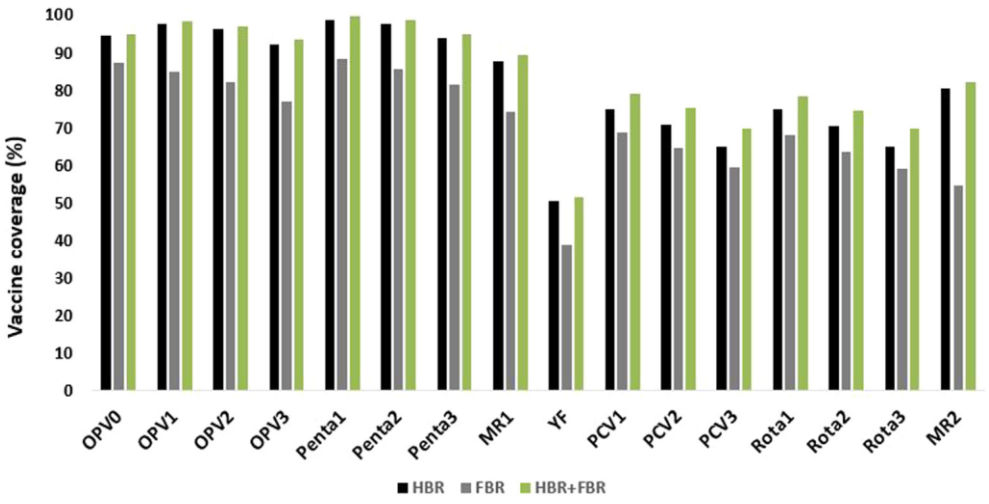


Fig. 5. Dose-specific coverage (%) by source of information, Burkina Faso, 2017BCG : Bacille Calmette et Guérin ; OPV : oral polio vaccine ; Penta : tetanus, whole cell pertussis, hepatitis B and Haemophilus influenzae type b ; Rota: rotavirus vaccine; PCV: pneumococcal conjugate vaccine; MR: measles-rubella; YF: yellow fever. HBR: home-based record; FBR: facility-based record. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is not unexpected, given that inappropriate HBRs can make the identification of recording fields challenging, thereby leading to incomplete recording, if at all [16]. This was particularly the case for the pneumococcal and rotavirus vaccine series. Given the co-administration of these vaccines with pentavalent vaccine, some vaccinators might assume that recording the latter is enough to document all concomitant vaccinations. However, even in the presence of co-administration, each vaccine dose should be recorded separately for clarity, in the eventuality of separate administrations due to logistical constraints [11]. Such inadequate recording practices have also been documented elsewhere [14], including DRC, Nepal, Benin, and Zimbabwe [31].

Besides the moderate agreement between HBRs and FBRs, we generally documented poor NPV of the latter when the former

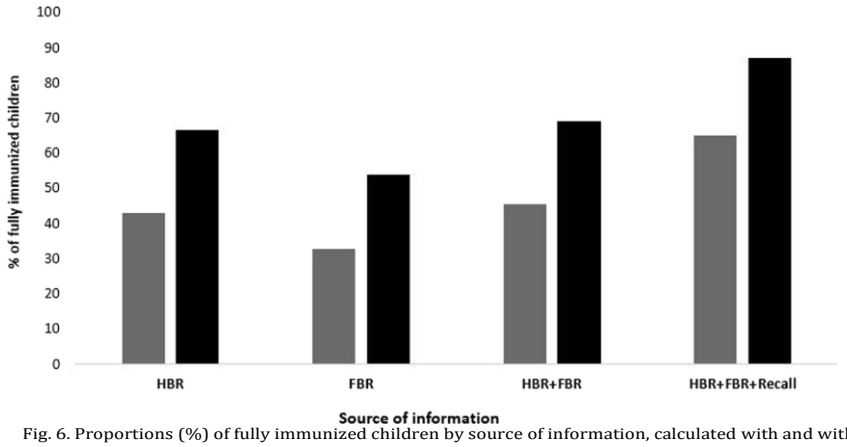


Fig. 6. Proportions (%) of fully immunized children by source of information, calculated with and without yellow fever (YF) vaccine, Burkina Faso, 2017. Note: history was collected for only pneumococcal and rotavirus vaccines. HBR: home-based record; FBR: facility-based record.

was taken as reference. Yet, for the pneumococcal and rotavirus series which were more likely to be under-recorded on HBRs, the NPV was fairly high, hovering around 70%. This indicates the potential added value of triangulating vaccination information from different sources in the determination of vaccination status [32,33]. As shown is our data, this may yield up to 5 percentage points compared to when HBRs alone are used. Estimates from lower-middle income countries have found higher coverage by HBRs compared to FBRs [18], corroborating our similar finding. Conversely, in high-income countries, estimates by FBRs were greater [19].

Given the pitfalls observed with HBRs and FBRs, complementing them with vaccination information obtained from caregiver's recall in the estimation of VC is appealing and this approach if often used in coverage surveys [34,35]. However, there is no consensus as to the value and use of recall in coverage surveys [12], given the risk of information bias which increases with the complexity of routine immunization schedules [20]. Studies comparing recall to FBRs [19] or to HBRs [17] have found poor agreement. Other studies, how- ever, reported substantial agreement between recall and HBRs in Ethiopia [36] and Tanzania [37], and suggested their use to comple- ment cards in ascertaining vaccination status.

Poor recording of vaccination information will likey lead to misclas- sification of vaccination status, and ultimately to biased estimations of VC locally and globally [14]. Therefore, addressing the identified issues should be given priority in Burkina Faso as well as other African countries with frequent new vaccine introductions and likely to have sim- ilar issues, as shown by a recent HBR-centered intervention led by John Snow Inc. in Africa [31]. Most data improvement interventions pertain to governance, tools and workforce [9].

In the short term, under the leadership of the government, the following actions can be implemented [11,15,28]: participatory planning involving all stakeholders, including community mem- bers, and technical and funding agencies; regular redisign and pretesting of HBRs and FBRs as the routine schedule evolves; ensuring continuous supply of HBRs which should be considered as an essential commodity; training and/or supportive supervision of health workers; implementation of job-aids; and field monitor- ing followed by use of data for timely decision-making.

Longer term actions could include working towards the implementation on an electronic immunization registry to optimize service delivery, allowing functionalities such as tracking child vaccination records from multiples sources, reminder of overdue vaccinations, and simplified reporting [38–40]. Still, careful operational and strategic planning and advocacy are essential to secure funding and political will to ensure sustainability.

Very few studies in low-income countries have investigated the quality of recording forms for individual vaccination data and its potential impact on the estimation of VC. Yet, most coverage surveys rely on written records to determine individual vaccination status [20,35]. Thus, the originality of this work is the systematic evaluation of the characteristics of current vaccination recording forms and their usefulness in estimating VC.

This evaluation was conducted in 10 low-performing districts targeted by the GHSA initiative. Therefore, our findings likely underestimate documentation and coverage in the other parts of the country. Other limitations also include the non-probabilistic sampling used to select HFs and participants, the single data entry, taking only sample pictures, and HBR assessment focused solely on the presence of recording fields for recommended vaccine doses while a broader set of criteria could have been examined [11,41].

3. Conclusion

The current assessment of some characteristics and completion of vaccination HBRs and FBRs in the routine immunization program in Burkina Faso adds to the limited but growing literature on the ascertainment of individual vaccination information, an essential consideration in vaccine coverage surveys. It uncovered a range of issues, including the lack of standardization of recording forms, the inconsistent filling of HBRs following vaccine administration, and discordant vaccination status, resulting into discrepant coverage estimates between HBRs and FBRs. Concerted efforts under government leadership should be implemented in the near term to address these issues, including regular update of immunization documents. Beyond Burkina Faso, such actions are also relevant for other countries with dynamic immunization schedules where the introduction of new vaccines occurs oftentimes. Future research on recording forms should include systematic picture taking and assess other quality elements beyond vaccination recording fields.

Declaration of Competing Interest

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

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Authors' contributions

Conceived and designed the study: EB, LK, WK, and IM. Performed data collection: LK, FS, MMB; analyzed the data: LK, FS, and EB; drafted the paper: LK and EB; critically reviewed the draft manuscript: CZM, FS, MMB, WK, TAE, AG, AGL, and IM.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.02.023.

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Impact of 13-valent pneumococcal conjugate vaccine on the incidence of hospitalizations for all-cause pneumonia among children aged less than 5 years in Burkina Faso: An interrupted time-series analysis

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ABSTRACT

Background: Pneumococcal disease is a major public health concern globally and particularly in Burkina Faso, where the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced nationwide into the routine immunization schedule in 2013. The aim of this study was to evaluate vaccine impact on all-cause pneumonia hospitalizations among children <5 years of age.

Methods: Hospitalization data covering a 10-year period (January 1, 2009–December 31, 2018) were collected retrospectively in four rural district hospitals, using medical records to extract data on relevant variables. Using an interrupted time-series design and segmented regression, the effectiveness and impact of PCV13 on the rates of pneumonia hospitalization were estimated. Severe acute malnutrition and unintentional injury were used as control conditions.

Results: Vaccine effectiveness was found to be 34% (95% confidence interval (CI) 16–49%, $p = 0.001$), 24% (95% CI 2–41%, $p = 0.032$), and 50% (95% CI 30–64%, $p < 0.001$) against all-cause pneumonia among children <5 years, <2 years, and 2–4 years of age, respectively. By October 2018, PCV13 introduction had led to an absolute reduction in the pneumonia hospitalization rate of 348 cases per 100 000 person-years among children <5 years of age. No decline was observed for the control conditions.

Conclusions: These estimates point to a substantial public health impact of PCV13 against pneumonia hospitalization among children aged <5 years in Burkina Faso.

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1. Introduction

Pneumococcal disease is characterized by diverse clinical manifestations, but the overall burden is dominated by pneumonia, which accounted for 15% of all paediatric deaths in 2017 (World Health Organization, 2019). Furthermore, up to 81% of pneumonia deaths occur in the first 2 years of life, and nearly all pneumonia deaths are recorded in low- and middle-income countries, with Sub-Saharan Africa bearing a great share of the pneumonia burden (43% of global pneumonia deaths) (Walker et al., 2013). In 2016, pneumonia was the third most frequent cause of hospital outpatient clinic visits in Burkina Faso, representing 5.4% of all visits (Ministère de la Santé, 2017). Although other pathogens, including viruses and fungi, may contribute to pneumonia, *Streptococcus pneumo- niae* is the most common cause of bacterial pneumonia

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and of vaccine-preventable severe pneumonia (World Health Organization, 2019).

On October 31, 2013, Burkina Faso introduced the 13-valent pneumococcal conjugate vaccine (PCV13) into its routine immunization programme, based on a three-dose schedule at 6, 10, and 14 weeks of age (World Health Organization, 2013). Many studies have reported significant reductions in the burden of pneumococcal disease following the introduction of pneumococcal conjugate vaccines (PCV), including invasive pneumococcal disease (Hammitt et al., 2019) and pneumonia (Silaba et al., 2019; Mackenzie et al., 2017; Grijalva et al., 2007). Given that the protective effects of PCVs may depend on the country-specific context, post-introduction studies have been set up to assess the impact of PCV13 in Burkina Faso. A recent study using national surveillance data reported the early impact of PCV13 and showed a 52% reduction in the incidence of vaccine-type pneumococcal meningitis (Soeters et al., 2019).

The aim of this study was to evaluate the effectiveness and impact of PCV13 introduction on all-cause pneumonia hospitalizations in children <5 years of age.

1. Methods

1.1. Study sites

The study was conducted in four district hospitals (Fig. 1): Séguénéga (Northern Burkina region), Nouna (Boucle du Mouhoun region), Orodara and Ndorola hospitals (Hauts-Bassins region); these are the reference hospitals for the health districts of the same names. Ndorola health district was created in 2016 and took over 14 of the 47 primary health facilities of Orodara. For comparability of the periods before and after PCV introduction, the data from Ndorola and Orodara were pooled and the results reported according to the pre-2016 district boundaries.

The selection of these sites was based on a convenience sampling approach that took into account the availability of a good quality archiving system for patient records over the entire study period (January 1, 2009–December 31, 2018), while attempting to represent the country's geographic diversity.

In Burkina Faso, the health personnel in district hospitals include physicians (general practitioners) who are responsible for the clinical management of patients (Ministère de la Santé, 2016a), in collaboration with nurses. The diagnosis of pneumonia in district hospitals is essentially based on clinical signs; due to limited availability, X-ray and pulse oximetry are not systemati- cally performed.

1.2. Data collection

In each district hospital, the data collection for both pneumonia and control conditions (severe acute malnutrition and unintentional injury) was conducted by local health personnel under the supervision of the district chief medical officer and the regional health director. Before data collection started, the data collectors were trained on study procedures by the team of investigators. Variables were systematically collected from hospital admission records (patient charts and hospitaliza- tion logbooks) using a case report form (CRF); these included general information (chart number, date of birth/age, sex, date of hospitalization, date of discharge, etc.) and clinical data (diagnoses at admission and discharge, symptoms, and outcome of hospitalization). Patients residing outside the catchment area of each district hospital were not included. All CRFs were monitored for completeness and accuracy, and validated by a clinical research associate.

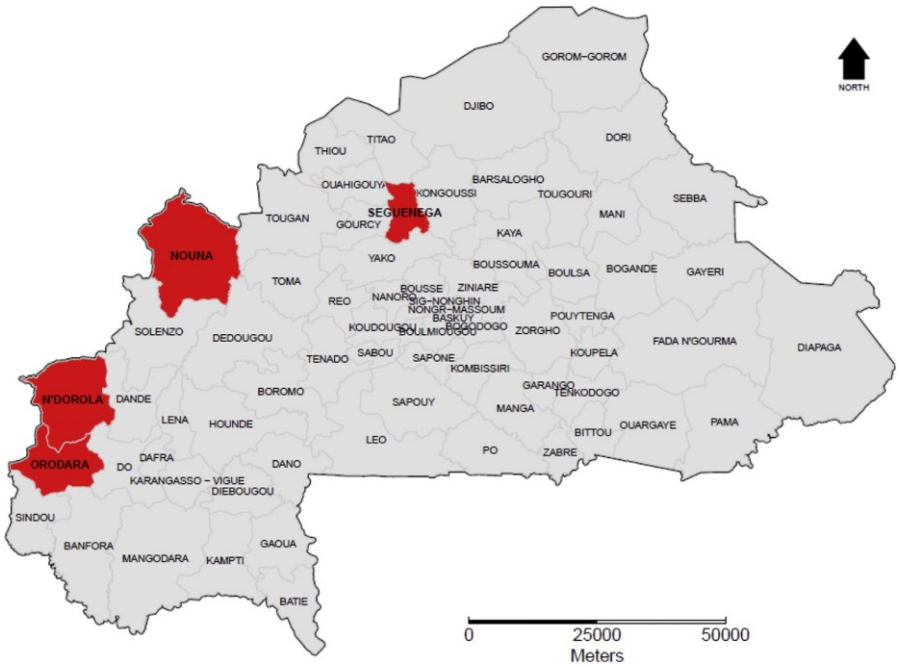

Fig. 1. Map of Burkina Faso with the selected health districts, 2019. The study health districts are shown in red.

To monitor the evolving access to health services in the country, monthlycountsofall-causehospitalizationsforchildrenunder 5 years were obtained from the statistics unit of each district hospital.

1.1. Case definitions

Clinical pneumonia was defined as a patient with a clinical diagnosis of acute lower respiratory infection (ALRI), severe ALRI, pneumonia, severe pneumonia, bronchopneumonia, severe bron- chopneumonia, bronchiolitis, or pleural effusion (Gatera et al., 2016) at hospital admission or discharge.

Severe pneumonia was defined as a patient with a clinical diagnosis of severe pneumonia/ALRI (with mention of the term 'severe' in the records reviewed), or clinical pneumonia (with no mention of the term 'severe') plus a qualitative statement in the records that one of the following signs of severity was present: chest indrawing, respiratory distress, hypoxia, cyanosis, convulsions, lethargy, prostration, or coma (World Health Organization, 2005).

Severe acute malnutrition (SAM) and unintentional injury (UI) were used as control conditions. For these, the definition was met when the medical records mentioned them as clinical diagnoses at entry or discharge. UI included injuries resulting from domestic events (e.g., falls, burns, and drowning) and from other events such as road traffic accidents. Due to the potential for overlap between malnutrition and pneumonia, when both conditions were present, the patient was considered to be a pneumonia case only, as done in a previous study (Silaba et al., 2019).

1.2. Data management

A database was developed on an OpenClinica platform, into which data were entered manually by clerks. A data manager periodically cleaned the data based on predefined criteria and queries generated by the principal investigator.

1.3. Demographic data

Official population data for each health district, as published in the annual statistics reports of the Ministry of Health, were used. To obtain monthly denominators, starting from January 1, 2009, the monthly population increments were first determined by dividing the annual total population absolute increase by 12, and then this increment was added to the population of month n to get that of month $n + 1$. Monthly populations were divided by 12 to obtain monthly denominators in person-years.

1.4. Vaccine uptake

In 2015, the administrative coverage for three PCV doses was 108.2% in Nouna, 97.7% in Orodara, and 108.3% in Séguénéga health districts (Ministère de la Santé, 2016b). The patient records did not have individual PCV vaccination information, so PCV eligibility was defined based on age. Any child who was 3 months of age or younger at the time of PCV introduction and 3 months of age or older during hospitalization was considered eligible to have received at least one PCV dose.

1.5. Statistical analyses

Monthly disease counts and incidence rates were used as the outcomes of interest. Descriptive analyses were first run, and then overall, pre- and post-PCV trends were generated, adjusting for seasonality. The period running from January 1, 2009 through October 31, 2013 (day of PCV13 introduction) was defined as pre-PCV. The first 14 months following introduction (November to December 2013 plus all 12 months of the year 2014) were considered as the vaccine deployment phase and excluded from time-series modelling. Thus, the post-PCV period was defined as January 1, 2015 to December 31, 2018.

For each age group (<5, <2, and 2–4 years), segmented regression analyses were performed to model disease-specific hospitalization rates before and after vaccine introduction. Given the absence of a catch-up campaign, both a change in intercept (immediate vaccine effects) and a change in slope (gradual vaccine effects) were hypothesized (Bernal et al., 2017). Thus, the model included time period (pre- vs post-vaccine), calendar month (to control for seasonality), time (to control for pre-existing trends), an interaction term PCV×time (to capture any change in trend), and a binary variable representing the free care policy fully implemented in the whole country since January 1, 2017 (World Health Organization, 2018). A generalized linear model was applied, using log-transformed admission rates as outcomes, with a Poisson distribution, scaling accordingly to account for over-dispersion. Model checking was conducted, and first-order autocorrelation was adjusted for when appropriate (Bernal et al., 2017). Modelling results were then used to estimate vaccine effectiveness as 1−IRR (incidence rate ratio) for the different outcomes. The predicted incidence rate for each outcome in October 2018, i.e., 5 years after PCV introduction, was derived. The expected incidence rates (those that would have been observed in the absence of the PCV programme) were then obtained by dividing the predicted incidence by the exponentiated sum of the coefficients for the variables PCV13 and PCV13×time (interaction term). Finally, the absolute incidence reduction was obtained as the difference between the expected and predicted incidence rates in October 2018.

Statistical significance was met for p-values < 0.05. All analyses were performed using Stata (version 13; StataCorp, College Station, TX, USA).

1.6. Ethical considerations

The study protocol was approved by the Comité d'Ethique pour la Recherche en Santé, the official body in charge of health research ethics in Burkina Faso.

1.7. Role of the funding source

The funder had no role in the study design, in the data collection, analysis, and interpretation, or in the writing of the final report. The first author had full access to all of the data, conducted all statistical analyses, and had final responsibility for the decision to publish.

2. Results

2.1. Sociodemographic and epidemiological characteristics of the patients

During the 10-year study period, the study hospitals recorded 5771 cases of pneumonia, of which 43.7% (n = 2520) met the definition of severe pneumonia. They also recorded 3444 cases of SAM and 438 cases of UI. With regard to sex, 57.0% (n = 3291) of pneumonia patients, 53.8% (n = 1444) of SAM patients, and 57.8% (n = 253) of UI patients were male. The lowest number of pneumonia cases was recorded in the month of June (n = 291 over 10 years) and the highest in October (n = 824 over 10 years). For all diseases, the majority (80% or more) of patients were admitted after referral or transfer from a peripheral health facility and 80% of patients were discharged normally (after recovery). Chest X-ray

Table 1
Sociodemographic and epidemiological characteristics of the study population, Burkina Faso, 2019.

Characteristic	Disease			
	All-cause pneumonia (*n* = 5771)	Severe pneumonia (*n* = 2520)	SAM (*n* = 3444)	UI (*n* = 438)
Hospital, *n* (%)				
Nouna	1716 (29.7)	636 (25.2)	1852 (53.8)	179 (40.9)
Orodara	1207 (20.9)	692 (27.5)	571 (16.6)	55 (12.5)
Séguénéga	2848 (49.4)	1192 (47.3)	1023 (29.6)	204 (46.6)
Male sex, *n* (%)	3291 (57.0)	1444 (57.3)	1851 (53.8)	253 (57.8)
Age group, *n* (%)				
0–23 months	3776 (65.4)	1721 (68.3)	2420 (70.3)	179 (40.9)
24–59 months	1995 (34.6)	799 (31.7)	1024 (29.7)	259 (59.1)
Home distance >10 km, *n* (%)	4050 (70.2)	1743 (69.2)	2942 (85.4)	314 (71.7)
Year of admission, *n* (%)				
2009	329 (5.7)	95 (3.8)	295 (8.6)	13 (3.0)
2010	337 (5.9)	130 (5.2)	222 (6.5)	20 (4.6)
2011	534 (9.3)	188 (7.5)	199 (5.8)	35 (8.0)
2012	632 (11.0)	257 (10.2)	255 (7.4)	33 (7.5)
2013	836 (14.5)	368 (14.6)	269 (7.8)	28 (6.4)
2014	595 (10.3)	264 (10.5)	381 (11.1)	55 (12.6)
2015	674 (11.7)	316 (12.5)	534 (15.5)	59 (13.5)
2016	436 (7.6)	212 (8.4)	451 (13.1)	54 (12.3)
2017	650 (11.3)	289 (11.5)	391 (11.4)	39 (8.9)
2018	748 (13.0)	401 (15.9)	447 (13.0)	102 (23.3)
Month of admission, *n* (%)				
January	450 (7.8)	199 (7.9)	295 (8.6)	30 (6.8)
February	433 (7.5)	178 (7.1)	234 (6.8)	37 (8.4)
March	483 (8.4)	211 (8.4)	256 (7.5)	25 (5.7)
April	384 (6.7)	163 (6.5)	222 (6.5)	33 (7.5)
May	360 (6.2)	158 (6.3)	222 (6.5)	47 (10.7)
June	291 (5.0)	138 (5.5)	222 (6.5)	47 (10.7)
July	340 (5.9)	172 (6.8)	220 (6.4)	45 (10.3)
August	489 (8.5)	252 (10.0)	256 (7.4)	47 (10.7)
September	634 (11.0)	268 (10.6)	352 (10.2)	43 (9.8)
October	824 (14.3)	345 (13.7)	432 (12.5)	27 (6.2)
November	581 (10.1)	214 (8.5)	392 (11.4)	25 (5.7)
December	502 (8.7)	222 (8.8)	341 (9.9)	32 (7.3)
Mode of admission, *n* (%)				
Direct admission	927 (16.1)	439 (17.4)	296 (8.6)	90 (20.6)
Referral/evacuation	4827 (83.7)	2077 (82.5)	3138 (91.1)	346 (79.2)
In-hospital transfer	14 (0.2)	3 (0.1)	10 (0.3)	1 (0.2)
Mode of exit, *n* (%)				
Normal discharge	4993 (86.6)	2082 (82.7)	2757 (80.2)	349 (80.2)
Referral/evacuation	236 (4.1)	132 (5.2)	81 (2.4)	28 (6.4)
Death	442 (7.7)	264 (10.5)	362 (10.5)	36 (8.3)
Other	97 (1.7)	40 (1.6)	236 (6.9)	22 (5.1)

SAM, severe acute malnutrition; UI, unintentional injury.

was performed for only 1.6% of patients (*n* = 91). The case fatality rate was 7.7% for pneumonia and 10.5% for severe pneumonia (Table 1). The mean monthly hospitalization rate for pneumonia and the control conditions increased after PCV13 implementation. However, while this increase was negligible and statistically non-significant for pneumonia (+5.9%, $p = 0.56$), it was substantial and statistically significant for UI (+113.7%, $p < 0.001$) and SAM (+61.4%, $p < 0.001$) (Supplementary Material Table S1).

1.1. PCV eligibility status of patients admitted after PCV introduction

Amongthe 5771 pneumonia cases included in the analyses, 53.8% (*n* = 3103) were admitted after October 31, 2013. Of these, 64.0% (*n* = 1985) were eligible to have received at least one PCV dose; PCV eligibility was 71.7% (1436/2003) among the <2 years age group and 49.9% (549/1100) among those 2–4 years of age. After the defined PCV deployment period, these proportions increased to 74.7% (1874/2508), 81.5% (1325/1626), and 62.2% (549/882) among those <5 years, <2 years and 2–4 years of age, respectively. Overall PCV eligibility increased gradually, from 18.7% in 2014 to 90.1% in 2018 ($p < 0.001$) (Supplementary Material Table S3).

1.2. Trends for all-cause pneumonia, control conditions, and all-cause hospitalization

Before PCV introduction, the monthly incidence of all-cause pneumonia increased by 2% per month (IRR 1.020, 95% confidence interval (CI) 1.015–1.025, $p < 0.001$). After PCV introduction, no trend was observed (IRR 1.004, 95% CI 0.997–1.011, $p = 0.27$). For SAM, there was no trend pre-PCV (IRR 0.996, 95% CI 0.991–1.002, $p = 0.23$), and the post-PCV trend was significantly downward (IRR 0.992, 95% CI 0.987–0.997, $p = 0.003$). UI admissions increased 1% per month both pre-PCV (IRR 1.012, 95% CI 0.999–1.024, $p = 0.06$) and post-PCV (IRR 1.014, 95% CI 1.001–1.026, $p = 0.04$) (Fig. 2, Table 2). For all studied outcomes, including all-cause hospitalization, overall trends were significantly upward over the period 2009–2018 (Supplementary Material Table S2, Supplementary Material Figure S1).

1.3. PCV effectiveness

Among all children, the adjusted IRR for all-cause pneumonia hospitalizations when comparing the post-PCV period to the pre-PCV introduction period was 0.66 (95% CI 0.51–0.84, $p = 0.001$), yielding a vaccine effectiveness (VE) estimate of 34% (95% CI 16–

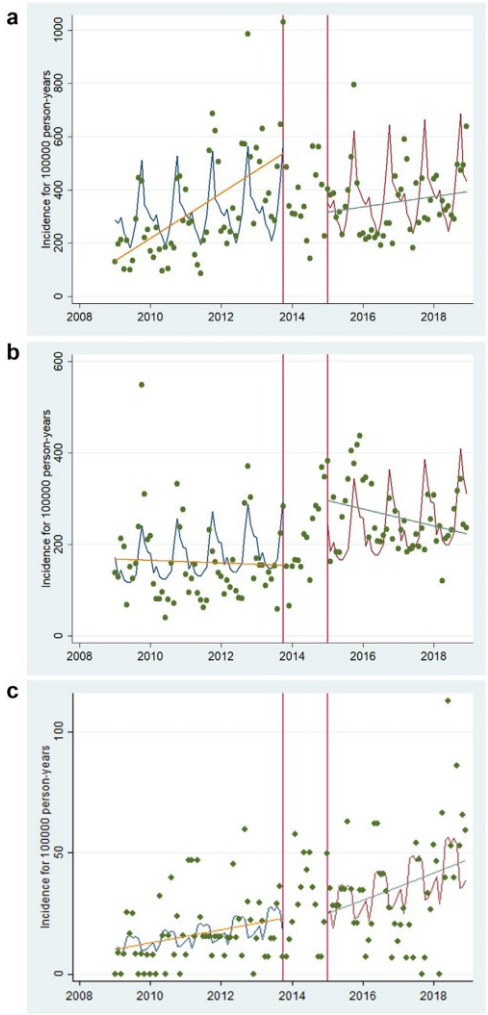

Fig. 2. Trends in monthly hospital admission rate for all-cause pneumonia (A), severe acute malnutrition (B), and unintentional injury (C) before (2009–2013) and after (2015–2018) PCV introduction among children aged less than 5 years in Burkina Faso.

- Dots: observed monthly incidence.
- Zigzagged lines: time series lines representing temporal trend over the study period (adjusted for season).
- Straight (fitted) lines: temporal trend before and after PCV13.
- Vertical lines: Nov. 1st, 2013 and Dec. 31st, 2014; they define the 14-month PCV deployment phase.

49%). In addition to this immediate VE, PCV introduction was also associated with a significant change in the baseline pneumonia trend (gradual vaccine effects), with a reduction in the monthly trend of 3.2% (IRR 0.968, 95% CI 0.955–0.982, $p < 0.001$). VE against severe pneumonia was 36% (95% CI 16–51%, $p = 0.001$) immediately post-PCV, and the change in monthly trend was similar to that seen for all-cause pneumonia. Immediate VE against pneumonia-related death was 51% (95% CI 22–69%, $p = 0.002$), and a significant monthly VE against this outcome was also seen (VE 3.5%, 95% CI 1.1–5.8%, $p = 0.004$).

As expected, PCV was not associated with UI admission rates, in terms of either an immediate or gradual rate reduction; the corresponding IRRs were 0.86 (95% CI 0.48–1.53, $p = 0.60$) and 1.025 (95% CI 0.996–1.054, $p = 0.09$), respectively. For SAM, PCV introduction was associated with a significant immediate increase in hospitalization rate (IRR 2.13, 95% CI 1.63–2.79, $p < 0.001$), but no significant trend change was documented (IRR 0.993, 95% CI 0.980–1.007, $p = 0.35$).

The effectiveness of PCV against pneumonia hospitalization among children <2 years old and those aged 2–4 years was generally similar to that observed among all children; however, a greater effect was seen among children aged 2–4 years. No decline was observed in the hospitalization rates for control outcomes in either of the two groups (Table 3).

Comparing the predicted incidence from the model to the expected incidence that would have been observed in the absence of the vaccine (counterfactual) in October 2018, an absolute reduction in the all-cause pneumonia incidence rate of 347.8 cases (95% CI 82.9–612.9) per 100 000 person-years was estimated among all children aged <5 years. The reductions for severe pneumonia and pneumonia-related death were 183.1 (95% CI 39.8–326.4) and 45.9 cases (95% CI 1.2 to 92.9) per 100 000 person-years, respectively (Supplementary Material Table S4).

1. Discussion

Five years after the introduction of PCV13 into the routine childhood immunization programme in Burkina Faso, it was found that the vaccine had had a significant impact on all-cause pneumonia hospitalizations among children <5 years of age. PCV13 was associated with a 34% reduction in pneumonia hospitalization rate. This effect increased over time, with an average of 3% fewer cases of pneumonia during each post-PCV month, after adjusting for seasonality and pre-PCV trends. This increase in VE over the post-PCV13 period is consistent with the increasing uptake of PCV13 in the paediatric population in the absence of a catch-up campaign, and also with a gradual amplification of PCV13 effects through both direct and indirect protection.

The introduction of PCV13 prevented an estimated 348 hospitalized pneumonia cases per 100 000 person-years among children age <5 years of age in October 2018. Applied to the < 5 years of age population in Burkina Faso of 3 599 550 children (Ministère de la Santé, 2019), this would translate to 12 526 pneumonia hospitalizations prevented annually. Numerous previous studies using time-series analyses have evaluated the impact of PCVs on all-cause pneumonia, predominantly in high-income countries, and the 34% VE estimated in the present study is similar to results from several of these. In a recent study among Kenyan children aged less than 5 years, VE against all-cause pneumonia for PCV10 implemented with a catch-up campaign targeting children <59 months was 27% (95% CI 3–46%) (Silaba et al., 2019). Likewise, a VE of 54% (95% CI 42–63%) against severe pneumonia (PCV7) was found in the same age group in Rwanda (Gatera et al., 2016). Among children aged <2 years, we found a VE of 24%, similar to studies in Sweden with 19% (Lindstrand et al., 2014) and 23% (Berglund et al., 2014) reductions, and the USA with a 21% reduction (Simonsen et al., 2014). Some studies, however, have found an even greater impact. In a landmark study in the USA, PCV7 led to a 39% (95% CI 22–52%) decline in clinical pneumonia hospital admissions in children <2 years of age during the first 4 years of implementation (Grijalva et al., 2007). Follow-up studies comparing late PCV7 years to pre-PCV years found a 43% decline in all-cause pneumonia among children aged <2 years (Griffin et al., 2013) and a 72% decline in all-cause pneumonia hospital admissions when comparing PCV13 to pre-PCV7 years (Griffin et al., 2014). In Australia, Jardine et al. (2010) found a 38% reduction in this age group.

Table 2:
Trend analyses for all-cause pneumonia, unintentional injury, and severe acute malnutrition before and after PCV introduction, Burkina Faso, 2009–2018.

Disease	Pre-PCV monthly trend (adjusted for season)		Post-PCV monthly trend (adjusted for season)	
	IRR[a] (95% CI)	*p*-Value	IRR[a] (95% CI)	*p*-Value
All-cause pneumonia				
0–59 months	1.020 (1.015; 1.025)	<0.001	1.004 (0.997; 1.011)	0.27
0–23 months	1.019 (1.014; 1.025)	<0.001	1.002 (0.995; 1.010)	0.56
24–59 months	1.022 (1.017; 1.027)	<0.001	1.008 (0.999; 1.017)	0.09
Unintentional injury				
0–59 months	1.012 (0.999; 1.024)	0.06	1.014 (1.001; 1.026)	0.04
0–23 months	1.006 (0.989; 1.023)	0.51	1.007 (0.991; 1.023)	0.39
24–59 months	1.016 (0.999; 1.034)	0.06	1.018 (1.000; 1.034)	0.02
Severe acute malnutrition				
0–59 months	0.996 (0.991; 1.002)	0.23	0.992 (0.987; 0.997)	0.003
0–23 months	0.999 (0.993; 1.005)	0.76	0.996 (0.991; 1.002)	0.21
24–59 months	0.991 (0.983; 0.999)	0.02	0.983 (0.975; 0.991)	<0.001

PCV, pneumococcal conjugate vaccine; IRR, incidence rate ratio; CI, confidence interval.
[a] These incidence rate ratios were derived from the model that included trend and season as independent variables.

Table 3
Incidence rate ratios for PCV introduction, Burkina Faso, 2019.

Disease	IRR for PCV13 introduction (change in intercept) IRR[a] (95% CI)	PCV effectiveness (immediate effect) VE[b] (95% CI)	*p*-Value	IRR for PCV13 introduction (change in slope) IRR[a] (95% CI)	PCV13 effectiveness (gradual effect, per month) VE[b] (95% CI)	*p*-Value
All-cause pneumonia						
0–59 months	0.66 (0.51; 0.84)	0.34 (0.16; 0.49)	0.001	0.968 (0.955; 0.982)	0.032 (0.018; 0.045)	<0.001
0–23 months	0.76 (0.59; 0.98)	0.24 (0.02; 0.41)	0.03	0.959 (0.945; 0.973)	0.041 (0.027; 0.055)	<0.001
24–59 months	0.50 (0.36; 0.70)	0.50 (0.30; 0.64)	<0.001	0.984 (0.967; 1.002)	0.016 (—0.002; 0.033)	0.08
Severe pneumonia						
0–59 months	0.64 (0.49; 0.84)	0.36 (0.16; 0.51)	0.001	0.970 (0.956; 0.984)	0.030 (0.016; 0.044)	<0.001
0–23 months	0.74 (0.56; 0.98)	0.26 (0.02; 0.44)	0.04	0.959 (0.944; 0.974)	0.041 (0.026; 0.056)	<0.001
24–59 months	0.45 (0.30; 0.68)	0.55 (0.32; 0.70)	<0.001	0.996 (0.975; 1.018)	0.004 (—0.018; 0.025)	0.74
Pneumonia-related death						
0–59 months	0.49 (0.31; 0.78)	0.51 (0.22; 0.69)	0.002	0.965 (0.942; 0.989)	0.035 (0.011; 0.058)	0.004
0–23 months	0.60 (0.37; 0.99)	0.40 (0.01; 0.63)	0.05	0.945 (0.920; 0.971)	0.055 (0.029; 0.080)	<0.001
24–59 months	0.22 (0.08; 0.60)	0.78 (0.40; 0.92)	0.003	1.031 (0.980; 1.083)	—0.031 (—0.083; 0.020)	0.24
Unintentional injury						
0–59 months	0.86 (0.48; 1.53)	0.14 (—0.53; 0.52)	0.60	1.025 (0.996; 1.054)	—0.025 (—0.054; 0.004)	0.09
0–23 months	1.28 (0.62; 2.68)	—0.28 (—1.68; 0.38)	0.50	1.020 (0.985; 1.058)	—0.020 (—0.058; 0.015)	0.26
24–59 months	0.64 (0.30; 1.37)	0.36 (—0.37; 0.70)	0.25	1.030 (0.991; 1.069)	—0.030 (—0.069; 0.009)	0.14
Severe acute malnutrition						
0–59 months	2.13 (1.63; 2.79)	—1.13 (—1.79; —0.63)	<0.001	0.993 (0.980; 1.007)	0.007 (—0.007; 0.020)	0.35
0–23 months	1.95 (1.45; 2.62)	—0.95 (—1.62; —0.45)	<0.001	0.993 (0.978; 1.008)	0.007 (—0.008; 0.022)	0.35
24–59 months	2.71 (1.86; 3.96)	—1.71 (—2.96; —0.86)	<0.001	0.997 (0.979; 1.016)	0.003 (—0.016; 0.021)	0.78

PCV, pneumococcal conjugate vaccine; IRR, incidence rate ratio; CI, confidence interval; VE, vaccine effectiveness.
[a] These incidence rate ratios were derived from the full model that included vaccine period (pre/post PCV), trend (time since 01/01/2009 in months), an interaction term (vaccine period × time), calendar month (used as dummy), and free care (dichotomous) as independent variables.
[b] Vaccine effectiveness calculated as 1 — IRR.

Our estimates and those of others were greater than the VE obtained in pre-licensure clinical trials of PCV products. In the Gambian PCV9 individually randomized trial (IRT) (Cutts et al., 2005), VE against all-cause pneumonia was 7% (95% CI 1–12%). A South African IRT also using PCV9 (Madhi et al., 2005) found a VE of 16% (95% CI 9–23%). As noted in previous publications (Silaba et al., 2019; Grijalva et al., 2007), it is not unexpected that real-world studies post-PCV implementation find greater impact than IRT, inasmuch as the former measure overall vaccine effects, including indirect effects that have been well documented in the literature (Rodrigo et al., 2015), while the latter only capture direct effects from individual vaccination.

Our analyses showed important differences between crude and adjusted estimates of VE, illustrating the utility of the interrupted time-series methodology and of the inclusion of control conditions. The crude before-and-after PCV comparison of the mean monthly hospital admission rates for pneumonia found no difference in incidence between the two periods. However, this occurred in a context in which a free care policy was implemented nationwide from January 1, 2017, increasing hospitalization rates for all measured causes in the present study. Consequently, the final multivariate model that adjusted for key confounders such as baseline trend in incidence and free care policy, found substantial reductions in observed compared to expected pneumonia hospitalization incidence rates. Although affirming causality from statistical significance in observational studies always warrants caution, quasi-experimental designs such as interrupted time-series using appropriate segmented regression are considered relatively robust (Taljaard et al., 2014) and in some instances can yield results comparable to randomized controlled trials (Fretheim et al., 2013). PCV13 reduced the adjusted admission rates for all-cause pneumonia consistently across age groups, but not those of control outcomes, providing internal study validity. In addition, the present study results are consistent with the impact of PCV13 against pneumococcal meningitis in the country (Soeters et al., 2019) and against all-cause pneumonia in other settings (Silaba et al., 2019; Lindstrand et al., 2014; Berglund et al., 2014; Simonsen et al., 2014; Grijalva et al., 2007). We therefore contend that our results support a causal link between PCV13 introduction and subsequent declines in adjusted pneumonia hospital admission rates in Burkina Faso.

VE appeared greater among children aged 2–4 years compared to those aged < 2 years. This finding is striking, because the latter group includes a higher proportion of PCV-eligible children (81.5% vs 62.2%). Nonetheless, the absence of individual vaccination information (both groups included vaccinated and unvaccinated individuals) and the fact that PCV13 showed a greater effect against vaccine-type pneumococcal meningitis among children aged 1–4 years compared to those aged less than 1 year (VE of 77% vs 62%) (Soeters et al., 2019), suggest that our estimates are compatible with true VE in these age groups. Furthermore, the proportion of pneumonia cases caused by respiratory syncytial virus is higher in younger children (Shi et al., 2017), which may lead to lower PCV impact. Recent studies in Kenya (Silaba et al., 2019) and the United Kingdom (Shiri et al., 2019) have also found greater VE in children aged 2–4 years than in those <2 years of age.

Several biases could have affected the study data. Before PCV introduction, a strong upward trend in pneumonia hospital admission rates was observed, a trend that disappeared following PCV13 introduction. Should this increase be the result of reduced data availability for earlier study years, we might have overestimated VE. However, this is unlikely given that no record loss was reported during data collection, and trends were upward over the entire period for all studied outcomes, including all-cause hospitalization. Instead, these trends likely reflect a consistent improvement in access to health services over time, considering that the average number of contacts with health services per inhabitant (number of new consultants/total population) increased from 0.57 to 1.22, 0.45 to 1.07, 0.47 to 1.23, and 0.92 to 1.11 between 2009 and 2018 for the country, Nouna, Orodara, and Séguénéga, respectively (Ministère de la Santé, 2019; Ministère de la Santé, 2010). Moreover, a recent meta-analysis showed a 320% increase (from 5/1000 to 21/1000) in the rate of hospitalization for pneumonia between 2000 and 2015 in low-income countries, despite a decrease in pneumonia-related mortality (McAllister et al., 2019).

Similarly, an increase in SAM admission incidence was found after PCV introduction in the present study. To determine whether this was caused by PCV13 introduction, a sensitivity analysis was performed that assumed the PCV programme had started a year earlier, on October 31, 2012 (Supplementary Material Table S5). The results still showed a significant increase in the rate of admission for SAM when comparing the periods after and before that date, while no significant change was observed for pneumonia, suggesting that the increase in SAM was not causally related to PCV13 introduction. In fact, in response to the 2012 nutrition crisis in the Sahel region, concerted efforts led by international organizations helped scale up the Integrated Management of Severe Acute Malnutrition, a strategy that involves active case finding in the community (Unicef, 2013). This ultimately could have resulted in more hospitalizations for SAM in the country.

This study had a few potential limitations. Interrupted time-series analyses comparing periods before and after interventions assume that the pre-intervention trend would have continued in the absence of the intervention (Wagner et al., 2002). If this were not the case, we would have overestimated VE, given that the pre-PCV13 period had an upward trend and the post-PCV13 period had no temporal trend. While the control conditions support the notion that overall hospitalization trends did not bias our results, interventions other than PCV13 (such as changes in antibiotic use policies) could have specifically affected pneumonia hospitalization. However, we are not aware of any such interventions at the national or regional level. Additionally, this study was limited to children under the age of 5 years and does not provide information on indirect protection of older children and adults. Future studies should include a wider age range to obtain further insights into the impact of PCV in the general population.

Conclusion

In conclusion, using segmented regression analyses in an interrupted time-series design and data collected over a 10-year period, a significant impact of PCV13 on all-cause pneumonia hospitalizations was found among children <5 years of age in Burkina Faso. Vaccine effectiveness was also observed against severe pneumonia and pneumonia deaths. These results are in line with those of previous studies using the same analytical methods and encourage the sustained use of PCV13 — or of new PCVs with broader serotype coverage — in the routine immuniza- tion schedule as a means of reducing the burden of childhood pneumonia.

Funding source

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Conflict of interest

JCM and BDG initiated the study while at the Agence de Médecine Préventive, but are now employed by Pfizer, Inc.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.03.051.

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The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Pneumococcal Carriage in Burkina Faso After 13-Valent Pneumococcal Conjugate Vaccine Introduction: Results From 2 Cross-sectional Population-Based Surveys

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Background. Burkina Faso, a country in Africa's meningitis belt, introduced 13-valent pneumococcal conjugate vaccine (PCV13) in October 2013, with 3 primary doses given at 8, 12 and 16 weeks of age. To assess whether the new PCV13 program controlled pneumococcal carriage, we evaluated overall and serotype-specific colonization among children and adults during the first 3 years after introduction.

Methods. We conducted 2 population-based, cross-sectional, age-stratified surveys in 2015 and 2017 in the city of Bobo-Dioulasso. We used standardized questionnaires to collect sociodemographic, epidemiologic, and vaccination data. Consenting eligible participants provided nasopharyngeal (all ages) and oropharyngeal (≥5 years only) swab specimens. Swab specimens were plated onto blood agar either directly (2015) or after broth enrichment (2017). Pneumococci were serotyped by conventional multiplex polymerase chain reaction. We assessed vaccine effect by comparing the proportion of vaccine-type (VT) carriage among colonized individuals from a published baseline survey (2008) with each post-PCV survey.

Results. We recruited 992 (2015) and 1005 (2017) participants. Among children aged <5 years, 42.8% (2015) and 74.0% (2017) received ≥2 PCV13 doses. Among pneumococcal carriers aged <1 year, VT carriage declined from 55.8% in 2008 to 36.9% in 2017 (difference, 18.9%; 95% confidence interval, 1.9%–35.9%; $P = .03$); among carriers aged 1–4 years, VT carriage declined from 55.3% to 31.8% (difference, 23.5%; 6.8%–40.2%; $P = .004$); and among participants aged ≥5 years, no significant change was observed.

Conclusion. Within 3 years of PCV13 implementation in Burkina Faso, we documented substantial reductions in the percentage of pneumococcal carriers with a VT among children aged <5 years, but not among persons aged ≥5 years. More time, a change in the PCV13 schedule, or both, may be needed to better control pneumococcal carriage in this setting.

Keywords. *Streptococcus pneumoniae*; survey; carriage; serotypes; pneumococcal conjugate vaccine; Burkina Faso.

Streptococcus pneumoniae (pneumococcus) is a major cause of disease and death globally [1, 2]. Persons who acquire pneumococci in their upper respiratory tract may develop clinical disease or, more likely, become asymptomatic carriers [3]. Healthy pneumococcal carriers are responsible for most transmission of pneumococci between persons. Therefore, carriage plays a critical role in the epidemiology of pneumococcal disease. Pneumococcal conjugate vaccines (PCVs) prevent carriage of vaccine serotypes and have proven very effective in reducing the burden of pneumococcal disease, even among unvaccinated contacts of vaccine recipients–so called indirect effects or "herd immunity" [4–6].

The 13-valent PCV (PCV13) was introduced into Burkina Faso in October 2013 with 3 primary doses given to infants at age 8, 12, and 16 weeks without a booster ("3 + 0" schedule) or a catch-up campaign [7]. Postintroduction studies are needed to fully understand the effects of the vaccine and provide scientific evidence to decision makers on whether adjustments in the PCV program are needed to better control pneumococcal disease. An analysis of national bacterial meningitis surveillance data collected in the first years after PCV13 introduction suggested that the PCV13 program reduced the pneumococcal meningitis burden in the country [8], but vaccine effects on carriage have not yet been reported.

Before PCV13 introduction (2008), a pneumococcal carriage survey was conducted in the city of Bobo-Dioulasso [9], providing useful baseline data to monitor vaccine effectiveness. Subsequently, we conducted 2 cross-sectional

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population-based surveys of pneumococcal carriage in the same city, approximately 1 year (March 2015) and 3 years (March 2017) after PCV13 introduction. We summarize data from these 2 studies, and through comparisons with published pre-PCV carriage data from 2008, estimate the impact of PCV13 against vaccine-type (VT) pneumococcal carriage in the region.

METHODS

Study Design and Participants

Each study (2015 and 2017) was a population-based cross-sectional survey conducted in the city of Bobo-Dioulasso, located in western Burkina Faso. We aimed to recruit 1000 participants per survey, with 200 participants in each of the following age groups: 0–11 months (1–11 months in 2017), 12–23 months, 24–59 months, 5–14 years and ≥15 years.

Similar to the 2008 survey, the 2015 and 2017 surveys used an age-stratified cluster sampling method to recruit participants. Ten urban districts (of the 21 that existed at the time of the 2008 survey) were randomly selected [9]. For each of these districts, 20 crossroads were randomly identified to serve as starting points. From each starting point, a street was randomly selected, and all the compounds along that street were visited by field workers, starting from the first compound on the left-hand side of the street.

A representative of each of the 5 age groups was recruited in each compound. If there were >2 representatives for the same age group, 1 was selected at random. If an age group was not represented in a given compound, field workers proceeded to the next compound in search of eligible subjects. Participants could be from the same family or not, depending on the composition of the household (we did not track clustering by family). Eligible subjects who consented to participate were screened by a questionnaire and then referred to the clinic of the Centre Muraz (https://www.centre-muraz.bf) for collection of nasopharyngeal (NP) (all ages) and oropharyngeal (OP) swabs (participants ≥5 years of age only).

Data Collection

After informed consent was obtained, a standardized questionnaire was administered to the parent or guardian of the participating child or to the participating adult. Questions included basic demographics, vaccine history, household characteristics (eg, number of persons living in the household, types of fuel used for cooking, and exposure to smoke), and socioeconomic variables. Children's vaccination histories were obtained from vaccination cards and included data on receipt of PCV13 and other routine immunizations. To obtain documented immunization histories, the study team reviewed immunization registers in health facilities for children whose vaccination cards were unavailable or failed to provide vaccination dates. During the visit for collection of NP and/or OP specimens, a second questionnaire was administered that included questions about current respiratory symptoms, recent illnesses, history of meningitis or pneumonia, and recent use of antibiotics.

Specimen Collection and Management

At the study clinic, NP and OP swab samples were collected by trained staff, following World Health Organization consensus methods [10]. OP swab samples were processed separately and collected in addition to NP swab samples to increase the efficiency of pneumococcal isolation. Samples were immediately placed into skim milk, tryptone, glucose, and glycerin (STGG) transport medium in appropriately labeled cryovials and placed on an icepack. On reaching the laboratory, inoculated STGG medium was vortexed for 10–20 seconds to disperse organisms from the swab sample. The samples were then either plated immediately (2015) or frozen at −80°C and processed later (2017).

Laboratory Procedures

For samples from 2015, 10 µL of STGG medium was directly streaked on a sheep blood agar plate containing 7% gentamicin. Samples from 2017 were first enriched by transferring 200 µL of STGG medium to 5.0 mL of Todd-Hewitt broth containing 0.5% yeast extract and 1 mL of rabbit serum. After incubation at 35°C–37°C for 6 hours, 10 µL of cultured broth was plated on sheep blood agar. Plates were incubated overnight at 37°C in a 5% carbon dioxide atmosphere. After 18–24 hours of incubation, pneumococci were identified by catalase, optochin susceptibility and bile solubility testing.

Isolates from the 2015 study were also confirmed using *lyt*A polymerase chain reaction (PCR) [11]. All *S. pneumoniae* isolates were stored in STGG medium at −80°C. To increase the sensitivity of pneumococcal detection, *lyt*A PCR testing was also performed on all STGG specimens collected in 2015 that were negative by culture; specimens that tested *lyt*A positive underwent repeated culture, and any pneumococci isolated were serotyped. Pneumococcal serotypes were determined for cultured isolates by a sequential multiplex conventional PCR assay [12]. All pneumococcal isolates determined to be nontypeable or for which the serotype was unclear by multiplex PCR were further tested by either a combination of real-time PCR [11] and Quellung (for 2015 isolates) or by Quellung reaction alone (for 2017 isolates).

Data Analyses

Definition of Vaccine and Nonvaccine Serotypes

The following serotypes, included in PCV13, were considered VTs: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. All other serotypes were categorized as nonvaccine types (NVTs).

Definition of a Valid Vaccination

Based on the PCV13 schedule in Burkina Faso, a valid dose was defined as a dose given at ≥8 weeks of age and ≥2 weeks before specimen collection. No intradose spacing requirement

was used; of note, all subjects but 1 (in 2017) had ≥4 weeks between doses.

Statistical Analyses

We used χ^2 or Fisher exact tests to compare proportions and t tests to compare means. Analyses were stratified by age group and vaccination status and accounted for the cluster sampling design. For the comparisons of data across all 3 surveys, we extracted 2008 (pre-PCV) overall and individual serotype carriage rates in specific age groups from the published results [9]. Vaccine impact was assessed by comparing the proportions of VT carriage among colonized individuals by age group between the pre-PCV survey (2008) and each of the post-PCV surveys (2015 and 2017). Differences were considered statistically significant at $P < .05$. All analyses were performed with Stata 13 software (StataCorp).

Ethical Approval and Consent to Participate

Ethical Approval and Consent to Participate

The 2 study protocols (2015 and 2017) were approved by the Ethics Committee for Health Research of Burkina Faso. In addition, the 2015 study, a collaboration between the Burkina Faso Ministère de la Santé and Agence de Médecine Préventive, was also reviewed and approved by the Commission Nationale de l'Informatique et des Libertés, France. The 2017 carriage study, a collaboration between the Burkina Faso Ministère de la Santé and the Centers for Disease Control and Prevention (CDC), was reviewed and approved by CDC's institutional human subjects review board. We systematically sought written informed consents from participants before questionnaire administration and sample collection.

RESULTS

Characteristics of Survey Participants

A total of 992 (8 participants had no laboratory results) and 1005 participants were enrolled and included in the analyses in 2015 and 2017, respectively. In 2015 and 2017, respectively, 45.5% and 44.4% of participants were male. Few adults aged ≥18 years were smokers (6.7% [8 of 119] in 2015 and 2.8% [5 of 182] in 2017); the proportions of persons who reported using antibiotics in the 2 weeks before the surveys were 5.0% and 11.2%, respectively. Coal was the fuel most frequently used in cooking (60.6% in 2015 and 83.1% in 2017) (Supplementary Table 1). For the 2008 survey, available demographic information was limited to the published data [9]. The 2008 study recruited participants up to age 39 years; the proportion of smokers among participants aged >14 years was 8.4%, and 43.7% of participants were male. By comparison, 45.4% and 45.2% of participants under age 40 years were male in 2015 and 2017, respectively.

PCV13 Eligibility and Coverage by Age Group

In 2015, a total of 321 participants, representing 32.4% of all participants and 53.8% of those <5 years of age, were eligible for at least ≥1 PCV dose. In 2017, these numbers were 511, 50.9%, and 84.6%, respectively. Among children aged <12 months, 68.2% (2015) and 71% (2017) had received ≥2 doses of PCV. Among children aged 12–23 months, the proportions with ≥2 doses of PCV were 62.4% and 97.9% in 2015 and 2017, respectively. Among all children aged <5 years, these proportions were 42.8% and 74.0%, respectively (Supplementary Table 2). The PCV status of some participants could not be ascertained because of the absence of written proof of vaccination, particularly among those aged 12–23 months; in this group, 6.1% and 26.6% of participants had unknown PCV status in 2015 and 2017, respectively.

Prevalence of Pneumococcal Carriage in 2015 and 2017

The prevalence of pneumococcal carriage among all study participants was 33.8% (95% confidence interval [CI], 30.8%–36.9%) in 2015 and 60.6% (57.4%–63.7%) in 2017, an increase likely due to different methods for pneumococcal detection for the 2 surveys (see Methods). Among children aged <12 months, pneumococcal carriage prevalences were 40.0% (95% CI, 33.4%–47.0%) in 2015 and 64.2% (57.2%–70.6%) in 2017 (Table 1), while VT pneumococcal carriage prevalences were 16.0% (11.6%–21.7%) (2015) and 23.9% (19.5%–30.3%)

Table 1. Overall and Vaccine-Type Pneumococcal Carriage Among All Study Participants, by Age Group and Survey Year, in Bobo-Dioulasso[a]

Age Group (No. in 2015/2017)	Participants With Pneumococcal Carriage % (95% CI)			
	All Carriage		VT Carriage	
	2015	2017	2015	2017
<1 y (200/201)	40.0 (33.4–47.0)	64.2 (57.2–70.6)	16.0 (11.6–21.7)	23.9 (19.5–30.3)
1 y (198/199)	53.0 (46.0–60.0)	73.4 (66.8–79.0)	19.7 (14.7–25.3)	20.6 (15.5–26.9)
2–4 y (199/204)	47.2 (40.3–54.3)	63.2 (56.3–69.6)	23.1 (17.7–29.6)	22.6 (17.4–28.7)
5–14 y (198/201)	20.7 (15.5–27.1)	65.2 (58.2–71.5)	7.6 (4.6–12.2)	28.9 (23.2–35.3)
≥15 y (197/200)	7.6 (4.6–12.3)	37.0 (30.5–44.0)	2.0 (0.8–5.3)	12.0 (8.2–17.2)
All ages (992/1005)	33.8 (30.8–36.9)	60.6 (57.4–63.7)	13.7 (11.7–16.0)	21.6 (18.9–24.5)

Abbreviations: CI, confidence interval; VT, vaccine-type.

[a]The 2015 and 2017 studies used different laboratory methods to detect carriage. Of 657 culture-negative samples from 2015 that were analyzed through *lyt*A, 85 (12.9%) were *lyt*A positive; repeated culture of these samples yielded 27 additional *Streptococcus pneumoniae* isolates.

(2017). Among children aged 1–4 years, pneumococcal carriage prevalences were 50.1% (95% CI, 45.0%–55.3%) in 2015 and 68.2% (63.6%–72.4%) in 2017; VT pneumococcal carriage prevalences were 21.6% (17.9%–25.8%) (2015) and 21.6% (17.8%–26.1%) (2017). The prevalences of VT carriage among all participants were 13.7% (95% CI, 11.7%–16.0%) and 21.6% (18.9%–24.5%) in 2015 and 2017, respectively, representing 40.6% and 35.6% of all pneumococcal colonization (Supplementary Table 3). Among infants aged <12 months who were colonized with *S. pneumoniae*, the percentage with a VT pneumococcus was lower in children who received 3 PCV doses than in those who received no doses in 2015 (37.7% vs 100%; $P = .03$), but not in 2017 (35.3% vs 40.0%; $P = .54$) (Table 2).

Changes in VT Pneumococcal Carriage Among Pneumococcal Carriers After PCV13 Introduction

Given that different laboratory methods were used to detect pneumococcal carriage among the 3 surveys, we analyzed the proportion of VT carriage among all pneumococcal carriers, by age group and study year (2008, 2015, or 2017) to evaluate the impact of PCV13 (Figure 1). Among infants aged <12 months, the percentage of pneumococcal carriers with a VT declined from 55.8% in 2008 (before PCV13 implementation) to 40.0% in 2015 (−28%) and 36.9% in 2017 (−34%) (difference between 2008 and 2017, 18.9%; 95% CI, 1.9%–~~0.~~35.9%; $P = .03$). Among children aged 1–4 years, the percentage of pneumococcal carriers with a VT declined from 55.3% in 2008 to 42.7% in 2015 (−23%) and 31.8% in 2017 (−42%) (difference between 2008 and 2017, 23.5%; 95% CI, 6.8%–40.2%; $P = .004$). There was no significant difference between surveys in the percentage of pneumococcal carriers with a VT in any of the other age groups, or in the survey population overall (Figure 1 and Supplementary Table 3).

Serotype Distributions

Serotype data from each post-PCV13 carriage survey were analyzed separately. More than 1 serotype was identified among 32 (3.2%) participants in 2015 and 14 (1.4%) participants in 2017. Among children aged <5 years, the 3 VT serotypes with the highest carriage prevalence in 2015 were 19F (4%), 6A (3.9%), and 23F (2.8%); in 2017, these were 19F (5.8%), 23F (5.3%), and 3 (3.3%) (Table 3). In these children, the proportions of carriers colonized with serotypes 23F, 6A, 14, 19A, and 4 declined between 2008 and 2017, whereas those with serotypes 19F and 3 were fairly stable (Supplementary Figure 1). For participants ≥5 years of age, the proportions of carriers colonized with serotypes 23F, 6B, 18C, and 9V declined between 2008 and 2017, whereas those with serotypes 19F, 3, and 4 increased (Supplementary Figure 2).

DISCUSSION

During 2017, approximately 3 years following introduction of the PCV13 into the national infant immunization program, we document a significant decline in the proportion of pneumococcal carriage due to PCV13 serotypes among children aged <1 year and 1–4 years compared with the pre-PCV period, with decreases of 34% and 42%, respectively. VT pneumococcal carriage persisted, however; approximately 20% of all participants still harbored VT pneumococci, as did about one-third of all children aged <1 year (37%) or 1–4 years (32%). Among participants ≥5 years of age, the proportion of pneumococcal carriers with a VT did not change significantly between 2008 and 2017, indicating that the infant PCV13 program had not stopped transmission of VT pneumococci among and to older children and adults, despite high national vaccine coverage, with 91% of children aged <12 months receiving 3 doses of PCV13 between 2014 and 2017 [13].

Overall and VT carriage prevalences were similar during 2008 [9] and 2015 but were higher in 2017 than in 2015. Because the 2017 laboratory procedures included a broth enrichment step shown to improve pneumococcal recovery [14, 15], the increase in overall pneumococcal carriage prevalence observed in 2017, 3 years after PCV introduction, was not unexpected. Nevertheless, when we evaluated the serotype distribution among pneumococci recovered, regardless of laboratory procedures used for overall detection of pneumococci (by estimating VT carriage among pneumococcal colonized individuals), our results were consistent with the literature. Indeed, as PCV programs mature and

Table 2. Vaccine-Type Pneumococci Among Pneumococcal Carriers Aged <5 Years by Vaccination Status and Age Group in Bobo Dioulasso, 2015 and 2017[a]

	2015				2017			
	No. With VT Carriage/Total (%)				No. With VT Carriage/Total (%)			
Age Group	0 Doses	1 or 2 Doses	3 Doses	*P* Value (3 vs 0 Doses)	0 Doses	1 or 2 Doses	3 Doses	*P* Value (3 vs 0 Doses)
<1 y	3/3 (100)	6/19 (31.6)	20/53 (37.7)	.03	2/5 (40)	15/31 (48.4)	24/44 (35.3)	.54
1 y	13/21 (61.9)	3/13 (23.1)	20/65 (30.8)	.01	0	1/6 (16.7)	30/98 (30.6)	NA
2–4 y	46/94 (48.9)	0	0	NA	20/42 (47.6)	3/8 (37.5)	17/54 (31.5)	.11

Abbreviations: NA, Not applicable; VT, vaccine-type.

[a]The 2015 and 2017 studies used different laboratory methods to detect carriage.

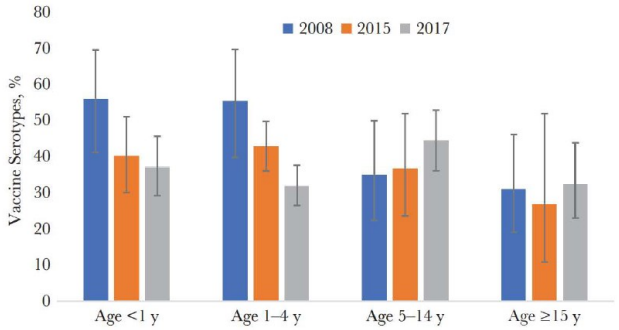

Figure 1. Proportions of vaccine-type carriage among all pneumococcal carriers by age group before and after 13-valent pneumococcal conjugate vaccine introduction in Bobo-Dioulasso, Burkina Faso. Error bars represent 95% confidence intervals.

vaccine coverage increases, many studies that used consistent methods over time have shown consistent declines in VT serotypes [5, 16–20].

Unlike the crude comparisons, VT carriage adjusted for pneumococcal detection rates declined between studies (2008, 2015, and 2017) among the partially vaccine-eligible group of participants aged ≤5 years. These reductions likely reflect the combined direct and indirect effects of PCV13 and add to the evidence on the effectiveness of PCVs in reducing VT carriage among children [5, 18, 21–25].

The declines in the percentage of pneumococcal carriers with a VT among children aged <5 years in our study are more modest than the 74% decline reported for the same age group in Kilifi, Kenya, after 5 years of implementation of a 10-valent PVC (PCV10) program that included a catch-up campaign targeting children <5 years old [5]. Unlike our study's finding, the authors also reported significant reductions among unvaccinated individuals in Kenya aged ≥5 years, demonstrating evidence of indirect protection among those too old to have been vaccinated. The indirect effect of PCV13 against VT carriage was also reported 3 years after implementation of a routine schedule in Malawi (including a catchup campaign targeting children <1 year old), with a 49% reduction in the percentage of pneumococcal carriers with a VT among mothers negative for human immunodeficiency virus [20]. The higher levels of reduction for Kenya and Malawi compared to Burkina Faso may reflect the benefit of conducting a catch-up campaign among children through age 5 years at the time of PCV introduction, a strategy that was not used in Burkina Faso.

Table 3. Distribution of Vaccine Serotype Pneumococci Among Children Aged <5 Years in Bobo-Dioulasso, 2015 and 2017[a]

Vaccine Serotype	Children, No. (%)	
	2015 (n = 597)	2017 (n = 604)
1	2 (0.3)	1 (0.2)
3	8 (1.3)	20 (3.3)
4	2 (0.3)	2 (0.3)
5	2 (0.3)	0 (0.0)
6A	23 (3.9)	13 (2.2)
6B	15 (2.5)	9 (1.5)
7F	1 (0.2)	0 (0.0)
9V	5 (0.8)	3 (0.5)
14	16 (2.7)	7 (1.2)
18C	2 (0.3)	7 (1.2)
19A	5 (0.8)	6 (1.0)
19F	24 (4.0)	35 (5.8)
23F	17 (2.8)	32 (5.3)
Total	**122 (20.4)**	**135 (22.4)**

[a]In 2015 and 2017, respectively, 318 (53.3%) and 200 (33.1%) specimens were pneumococcal culture negative among children aged <5 years; the numbers of nonvaccine serotypes in 2015 and 2017 were 163 (52.8%) and 244 60.4%), respectively. Note that laboratory methods used to detect carriage differed between 2015 and 2017.

Besides these observational studies, the value of catch-up campaigns has also been shown by mathematical modeling. Data from Vietnam [26] suggested that a catch-up campaign among children aged ≤5 years implemented at the time of PCV introduction would be very effective, leading to a further 38% reduction of invasive pneumococcal disease above that seen by routine vaccination alone, and to a near-eradication of VT carriage in the same age group. Likewise, using data from the Kilifi research platform in Kenya [27], Flasche et al [28] showed that a catch-up campaign among children aged ≤5 years would lead to the prevention of 42% more invasive pneumococcal disease cases compared with vaccinating only age-eligible cohorts within 10 years of PCV program implementation. In its position paper recommending the introduction of PCVs in routine immunization programs, the Strategic Advisory Group of Experts on Immunization, World Health Organization, stated that "Maximized protection at the time of introduction of PCV10 or PCV13 can be achieved by providing 2 catch-up doses at an interval of at least 2 months to unvaccinated children aged 12–24 months and to children aged 2–5 years who are at risk of pneumococcal infection" [29].

Our carriage study findings provide some context for early results on the impact of PCV13 against pneumococcal meningitis in Burkina Faso. Two years after introduction, the incidence of pneumococcal meningitis had declined significantly by 76% among children aged <1 year and by 58% among those aged 1–4 years; however, reductions among children aged 5–14 years and adults were not statistically significant [8]. Both the early carriage and the meningitis data suggest that, in contrast to effects reported from higher-income countries [30–32], vaccine serotypes continue to circulate in vaccinated and unvaccinated age groups 3 years after PCV13 introduction; this suggests that more time or alternative vaccination strategies might be needed for the full effect of the infant program to be observed in Burkina Faso.

Our data suggest little to no vaccine effect on vaccine serotypes 3 and 19F carriage in all participants. These observations are similar to those reported by in the Gambia 5 years after PCV introduction [33]. In Kilifi, Kenya, however, Hammitt et al [5] reported substantial reductions in carriage of all vaccine serotypes, possibly owing to the catch-up campaign at introduction. We also observed a consistent increase in the proportion of the nonvaccine serotype 35B following vaccine introduction in all participants, confirming similar findings in Kenya [5] and the Gambia [33]. However, pneumococcal meningitis caused by serotype 35B after vaccine introduction in Burkina Faso did not show an increase comparable to that of the carriage of this serotype [34].

Burkina Faso lies entirely within the African meningitis belt, which has a unique pneumococcal epidemiology, specifically high incidence of serotype 1 disease after age 2 years, as documented before [35] and after [34] PCV introduction. In neighboring Ghana, where PCV13 was introduced in 2012 on the same schedule as used in Burkina Faso (3 + 0 schedule, no catchup campaign), a serotype 1–dominated pneumococcal meningitis outbreak was recorded in 2015–2016 with many PCV-ineligible cases, suggesting little herd protection, if any at all, from Ghana's infant PCV13 program [36]. An infant PCV program, at least based on a 3 + 0 schedule, appears unable to control transmission of serotype 1 in meningitis belt countries [37].

In a phase IV immunogenicity trial comparing a "2 + 1" schedule (at age 6 weeks, 14 weeks, and 9 months) with the standard 3 + 0 schedule among infants in Burkina Faso, the booster dose elicited a robust memory response among its recipients; for instance, 99% of infants in the 2 + 1 schedule arm versus 75% of those in the 3 + 0 schedule had achieved putatively protective immunoglobulin G levels of 0.35 μg/mL against serotype 1 at 10 months of age [38]. These findings suggest that adding a booster dose to the infant schedule, as was recently done in Australia [39, 40], could improve control of pneumococcal carriage in Burkina Faso. However, this is speculative and even a late first year of life booster may have little impact on serotype 1 transmission among older persons.

Consistent with previous pneumococcal colonization studies [9, 41], carriage of serotype 1 in our study was very rare, contrasting with its frequent implication in pneumococcal meningitis. Consequently, it may be that unique schedules or approaches to immunization, such as a booster during later childhood or direct vaccination of a large segment of the population as was done for persons aged 1–29 years with serogroup A meningococcal conjugate vaccine [42, 43], are required to address serotype 1 in the meningitis belt. Indeed, while several years of implementation will be required to gather data on the effectiveness of shifting from the current 3 + 0 schedule to the 2 + 1 schedule (as already envisaged in Burkina Faso [44]), we have evidence from both empirical [5, 43] and modeling [26, 28] data that mass vaccination targeting a broader age group could rapidly lead to the control of pneumococcal carriage and disease. Eventually, irrespective of the dosing schedule, meningitis belt countries may need to implement at least one catch-up mass vaccination campaign to achieve maximal program impact. The financial feasibility and practical modalities of such campaigns have yet to be explored.

The following limitations should be considered in the interpretation of our findings. First, although all 3 studies have several common characteristics such as age-stratified probabilistic cluster sampling and sample collection during the dry season, there were some variations in laboratory procedures. Indeed, while direct plating was used in 2008 [9] (Quellung for serotype confirmation) and 2015 (real-time PCR and Quellung for serotype confirmation), broth enrichment of specimens preceded plating in 2017 (Quellung for serotype confirmation), and this may explain the differences observed in the crude carriage rates between 2017 and 2008 or 2015. We attempted to minimize this potential bias by adjusting for pneumococcal recovery rate, which consisted of calculating and comparing the percent carriage of individual serotypes or groups of serotypes among pneumococcal carriers. In so doing, we found meaningful results consistent with time, PCV introduction and the literature.

A second limitation was that all 3 studies were limited to sampling conducted in the urban setting of Bobo-Dioulasso, the second-largest city of Burkina Faso; thus, findings are not necessarily generalizable to the entire country, given that carriage often differs by setting, especially between urban and rural areas [41]. Third, the cross-sectional design added to the limited number of time points studied cannot fully account for temporal trends. Finally, as the vaccination status of some children could not be ascertained, this brings uncertainty to our estimation of vaccine impact.

In conclusion, 3 years after PCV13 introduction in Burkina Faso, we showed significant reductions in the percentage of pneumococcal carriers with a vaccine serotype among the partially vaccine-eligible group of children aged <5 years. However, we found no clear evidence of indirect effects (herd immunity) among children aged ≥5 years or adults.

Furthermore, in 2017, 1 in 5 children <2 years of age still harbored VT pneumococci. The lack of a catch-up campaign at the time of PCV13 introduction, the lack of a booster dose in the current PCV13 schedule, conditions in the meningitis belt that foster transmission, or a combination of multiple factors could explain the suboptimal clearance of vaccine serotypes among vaccine-eligible children and the absence of indirect effects against VT colonization. These findings, along with meningitis data, support consideration of changes in the implementation of PCV13 programs in Burkina Faso and similar settings.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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REVIEW

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Pneumococcal vaccine implementation in the African meningitis belt countries: the emerging need for alternative strategies

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ABSTRACT

Introduction: Besides meningococcal disease, the African meningitis belt (AMB) region is also affected by pneumococcal disease. Most AMB countries have introduced pneumococcal conjugate vaccines (PCV) following a schedule of three primary doses without a booster or a catch-up campaign. PCV is expected to help control pneumococcal disease through both direct and indirect effects. Whether and how fast this will be achieved greatly depends on implementation strategies. Pre-PCV data from the AMB indicate high carriage rates of the pneumococcus, not only in infants but also in older children, and a risk of disease and death that spans lifetime. Post-PCV data highlight the protection of vaccinated children, but pneumococcal transmission remains important, resulting in a lack of indirect protection for unvaccinated persons.

Areas covered: A non-systematic literature review focused on AMB countries. Relevant search terms were used in PubMed, and selected studies before and after PCV introduction were summarized narratively to appraise the suitability of current PCV programmatic strategies.

Expert opinion: The current implementation strategy of PCV in the AMB appears suboptimal regarding the generation of indirect protection. We propose and discuss alternative programmatic strategies, including the implementation of broader age group mass campaigns, to accelerate disease control in this high transmission setting.

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African meningitis belt; booster; catch-up campaigns; dosing schedule; impact; pneumococcal conjugate vaccines pneumococcal disease

1. Introduction

The African meningitis belt (AMB) is a set of 26 countries in Africa, stretching between Senegal (west) and Ethiopia (east) [1–3]. These countries are known for having a high annual incidence of bacterial meningitis, with *N. meningitidis* (meningococcus) implicated in large seasonal outbreaks [4,5,6–8]. Since the deployment of the serogroup A meningococcal conjugate vaccine in the region [9–11], meningococcal meningitis due to serogroup A has been brought to near elimination [12,13,14–17], although other serogroups (C, X and W) continue to cause large outbreaks [18,19,20–22].

A pentavalent meningococcal conjugate vaccine (containing serogroups A, C, Y, W, and X) is under development and could lead to sustainable control of meningococcal meningitis in the region [23,24,25]. Alongside the meningococcus, *S. pneumoniae* (pneumococcus) is another important etiology of bacterial meningitis in the AMB characterized by a high incidence [26,27], a high case fatality rate (CFR) [28–30], and affecting all age groups [27,31,32].

In addition, *S. pneumoniae* is a major cause of pneumonia in low-income countries, leading to large numbers of disease episodes, hospitalizations, and deaths [33,34,35–37]. To alleviate the burden of pneumococcal disease, countries of the AMB have introduced pneumococcal conjugate vaccines (PCV), with the support of Gavi, the vaccine Alliance [38,39]. Although catchup campaigns have been advised by the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) as part of introduction strategies [40], no other country of the AMB besides Kenya has conducted nationwide catchup vaccination at the time of PCV introduction into their routine schedule [41,42], possibly due to limited vaccine supply, costs and operational constraints. Early evidence on the direct effects of PCV in the AMB is encouraging, with significant reductions in disease and carriage in vaccinated cohorts [43,44–46]. However, indirect effects are manifesting more slowly, if at all [44,47]. Moreover, data from several studies in the AMB show that non-vaccine eligible individuals represent most cases of disease and deaths due to pneumococcal meningitis following PCV introduction [45,48]. More time may therefore be needed until we observe the full extent of direct and indirect protection of PCV under their current utilization strategy in the region. Alternatively, strategies such as directly vaccinating older age groups beyond early childhood with at least one PCV dose or providing a booster dose to the numerous birth cohorts who received only three primary PCV doses could accelerate the onset of herd immunity, prevent disease, and save numerous lives. Analyzing data from published key studies on the

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Article highlights

- In the African meningitis belt (AMB), the burden of pneumococcal disease is not only borne by infants <1 year but also by older children and adults, and tends to be dominated by serotype 1
- 23 of 26 AMB countries have introduced pneumococcal conjugate vaccines (PCV) in routine infant immunization schedule without a booster dose and without catch-up campaigns except in Kenya
- Epidemiological data on pneumococcal disease and carriage before and several years after PCV introduction in the AMB suggest the current infant-only PCV program may not be appropriate to control transmission in the near term
- We propose and discuss novel programmatic avenues to accelerate the control of pneumococcal disease in the AMB through both direct and indirect effects, including direct vaccination of broader age groups through catch-up campaigns.
- More work is needed to guide AMB countries on the cost-effectiveness and practical modalities of broader age group mass vaccination in their setting.

epidemiology of pneumococcal carriage and disease before and after the introduction of PCV, we suggest alternative implementation strategies, including broader age group mass vaccination campaigns, to accelerate the control of pneumococcal disease in the AMB.

2. Literature search, selection criteria, and summary of evidence

2.1. Search strategy

We searched PubMed for articles published in English or French until 30 September 2020. The search terms were the following:

(pneumococcal OR 'streptococcus pneumoniae' OR pneumococcus OR pneumococci) AND (meningitis OR pneumonia OR bacteriemia OR septicemia OR carriage OR mortality OR 'invasive pneumococcal disease') AND ('Africa, south of the Sahara' OR 'meningitis belt').

In addition, we repeated the search with the same terms, except that the study location term was replaced by the name of each of the 26 countries of the AMB, that is:

(pneumococcal OR streptococcus pneumoniae OR pneumococcus OR pneumococci) AND (meningitis OR pneumonia OR bacteriemia OR septicemia OR carriage OR mortality OR 'invasive pneumococcal disease') AND ('country name').

Additionally, relevant references from studies retrieved through the PubMed search were consulted.

2.2. Inclusion criteria

The inclusion criteria were the following:

- Study is not a review or a modeling or a redundancy.
- Study was conducted in the AMB before PCV introduction or presents pre-PCV data (for pre-PCV epidemiology description).
- Study has laboratory confirmed data on the pneumococcus, with serotyping results.
- Study was not performed in special populations, such as persons living with HIV or sickle-cell disease, and malnourished children.
- Study has incidence data with a population denominator for pneumococcal disease, or incidence or prevalence data for carriage, in at least one clearly defined age group.
- For post-PCV studies, study presents vaccine effectiveness (VE) data, or data that can allow for VE estimation in at least one clearly defined age group, vaccinated (direct effects) or not (indirect effects).

2.3. Summary of evidence

We provide a narrative synthesis of pre- and post-PCV data on pneumococcal disease and carriage in the AMB.

3. Epidemiology of pneumococcal carriage and disease in the African meningitis belt before the introduction of pneumococcal conjugate vaccines

Several studies have described the epidemiology of pneumococcal disease (Table 1) and carriage (Table 2) in the AMB before the introduction of PCV.

3.1. Carriage

Studies from Burkina Faso [49], The Gambia [50], and Nigeria [51] show a high prevalence of pneumococcal carriage, including vaccine-serotype carriage beyond infancy. For instance, carriage rates for 13-valent pneumococcal conjugate vaccine (PCV13) serotypes were 32% and 14% among 1–4 and 5–9 year-olds, respectively, in Burkina Faso (2008); and 17.7% among the 5–17 year-olds in The Gambia (2009).

3.2. Invasive pneumococcal disease

Surveillance data from Burkina Faso [49,52,53], Chad [54], Ghana [55], Mali [35], Niger [56], Senegal [57], and Togo [33] show a consistent pattern: the highest incidence is observed in infants <1 year, but all other age groups are at risk of pneumococcal meningitis. For instance, data from Ghana over the period 1998–2003 [55] show an average annual incidence of 43/100,000 among infants <1 year, and 15–26/100,000 among all other age groups >1 year. Given the large size of the population aged >1 year, this translates into much higher absolute numbers of cases among older children and adults.

As an illustration, a study from Burkina Faso showed that 82% of pneumococcal meningitis cases were >1 year [53]. Pneumococcal meningitis case fatality rate (CFR) in older children and adults is sometimes similar [33] to or greater [35] than in infants <1 year, resulting in more deaths in older age groups; for instance, about 3 in 4 pneumococcal meningitis deaths in Burkina Faso over the period 2002–2005 were individuals >1 year [52].

Table 1. Selected studies on the epidemiology of pneumococcal disease prior to the introduction of pneumococcal conjugate vaccines in the African meningitis belt.

Country	Author, year [ref]	Outcome	Study period	Design	Results			
					Annual incidence of pneumococcal disease by age group (per 100,000 populations)	Case fatality rate (%) by age group	Age distribution of pneumococcal disease cases n (%)	Age distribution of pneumococcal deaths (%)	Serotype 1 disease
Burkina Faso	Yaro,2006 [52]	Pneumococcal meningitis	2002–2005	Prospective surveillance	< 5 y: 33 5–14 y: 10 ≥ 15 y: 11	< 5 y: 53 5–14 y: 39 ≥ 15 y: 44		Number (%) of deaths due to Sp meningitis: < 1 y: 32 [28] ≥ 1 y: 82 [72]	Relative risk of serotype 1 among cases: ≥ 5 y vs <5 y (reference group): 2.1 (1.3–3.4)
Burkina Faso	Mueller,2012 [49]	Pneumococcal meningitis	2007–2009	Prospective hospital-based surveillance	0–5 mo.: 57.5 6–11 mo.: 43.1 1–4 y: 5.0 5–9 y: 10.6 10–14y: 8.9 15–19 y: 14.6 20–29 y: 5.6 30–39 y: 6.2 ≥ 40 y: 4.4				Serotype 1 meningitis per 100,000 0–5 mo.: 5.8 6–11 mo.: 3.6 1–4 y: 1.0 5–9 y: 6.2 10–14y: 5.8 15–19 y: 7.9 20–29 y: 3.4 30–39 y: 2.3 ≥ 40 y: 2.1
Burkina Faso	Kambiré, 2016 [53]	Pneumococcal meningitis	2011–2013	National prospective surveillance	<1 y: 26.9 1–4 y: 5.4 5–9 y: 7.1 10–14 y: 7.3 ≥ 40 y: 3.0		< 1 y: 276 [18] ≥ 1 y: 1252 [82]	Number (%) of deaths due to Sp meningitis: < 1 y: 88 [25] ≥ 1 y: 269 [75]	% of serotype 1 among Sp meningitis cases: <1 y: 12 1–4 y: 23 ≥5 y: 57
Chad	Soeters, 2019 [54]	Pneumococcal meningitis	2015–2017	Case-based national prospective surveillance	<1 y: 27.4 1–4 y: 6.3 5–9 y: 2.9 10–14 y:2.7 15–29 y: 0.5 ≥ 30 y: 2.5				
Gambia	Mackenzie, 2017 [64]	Radiological pneumonia	2008–2010	Health and Demographic Surveillance System	2–11 months: 2100 12–23 months: 1530 2–4 years: 520				
Gambia	Mackenzie, 2017 [64]	Pneumococcal pneumonia	2008–2010	Health and Demographic Surveillance System	2–11 months: 290 12–23 months: 260				
Gambia	Mackenzie, 2016 [44]	Invasive pneumococcal disease	2008–2010	Health and Demographic Surveillance System	2–23 months: 253 2–4 years: 113 5–14 years:12 ≥ 15 years:9				

(*Continued*)

Table 1. (Continued).

Country	Author, year [ref]	Outcome	Study period	Design	Annual incidence of pneumococcal disease by age group (per 100,000 populations)	Results			
						Case fatality rate (%) by age group	Age distribution of pneumococcal disease cases n (%)	Age distribution of pneumococcal deaths (%)	Serotype 1 disease
Ghana	Leimkugel, 2005 [55]	Pneumococcal meningitis	1998–2003	Prospective surveillance (Northern Ghana)	<1 y: 43 1–4 y: 20 5–14 y: 26 15–29 y:18 30–59 y: 15 ≥ 60 y: 23				
Mali	Campbell, 2004 [35]	Pneumococcal meningitis	2002–2003	Prospective hospital-based surveillance	0–11 mo.:43.0 1–4 y: 5.9 5–15 y: 2.5	0–11 mo.:23.4 1–4 y: 26.1 5–15 y: 9.1			
Mali	Campbell, 2004 [35]	Pneumococcal pneumonia	2002–2003	Prospective hospital-based surveillance	0–11 mo.:32.8 1–4 y: 10.0 5–15 y: 50.8	0–11 mo.:10.5 1–4 y: 30.0 5–15 y: 20.0			
Niger	Campagne, 1999 [56]	Pneumococcal meningitis	1981–1994	Retrospective surveillance data	<1 y: 149.6 1–4 y: 10.4 5–9 y: 6.4 10–14 y: 6.9 15–19 y: 9.0 20–29 y: 4.7 30–39 y: 3.2 ≥ 40: 7.9	<1 y: 57.7 1–4 y: 56.8 5–9 y: 15.8 10–14 y: 34.8 15–19 y: 62.1 20–29 y: 58.3 30–39 y: 20.0 ≥ 40: 60.0			
Senegal	Cadoz, 1981 [57]	Pneumococcal meningitis	1970–1979	Retrospective analysis of hospitalized cases	<1 y: 94.6 1–4 y: 16.6 5–9 y: 4.5 10–14y: 3.7 15–19 y: 2.4 20–29 y: 4.0 30–39 y: 5.2 40–49 y: 7.8 50–59 y: 11.0 60–69 y: 15.2 ≥ 70 y: 13.9				
Togo	Moïsi, 2017 [33]	Pneumococcal meningitis	2010–2013	Prospective hospital-based surveillance	< 1 y: 17.9 ≥ 1 y: 6.5	5 y: 34.6 ≥ 5 y: 34.6			% of serotype 1 among Sp meningitis cases: < 5 y: 8.3 ≥ 5 y: 52.5
Togo	Moïsi, 2017 [33]	Pneumococcal disease (meningitis and pneumonia)	2010–2013	Prospective hospital-based surveillance	<5 y: 7.5 ≥ 5y:14.8				

Sp: *Streptococcus pneumoniae*

Table 2. Selected studies on pneumococcal carriage prior to the introduction of pneumococcal conjugate vaccines in the African meningitis belt.

Country	Author, year [ref]	Study period	Design	Results	
				PCV10 serotypes carriage prevalence (%) by age group	PCV13 serotypes carriage prevalence (%) by age group
Burkina Faso	Mueller, 2012 [49]	2007–2009	Cross-sectional population-based survey		0–5 mo.: 31 6–11 mo.: 47 1–4 y: 32 5–9 y: 14 10–14y: 9 15–19 y: 8 20–24 y: 3 25–29 y: 3 30–39 y: 8
The Gambia	Yusuf, 2015 [50]	2009	Cross-sectional population-based survey		< 5 y: 46.8 5–17 y: 17.7 ≥ 18 y: 5.5
Nigeria	Adetifa, 2018 [51]	2016–2017*	Cross-sectional population-based survey	< 5 y: 44.1 5–17 y: 24.3 18–34 y: 13.8 35–49 y: 11.8 ≥ 50 y: 3.0	< 5 y: 62.4 5–17 y: 47.8 18–34 y: 18.6 35–49 y: 15.8 ≥ 50 y: 10.6

*There is some overlap between the study period and the introduction of PCV, but vaccine uptake was low at the time of the study.

Another hallmark of pneumococcal meningitis in the AMB is the domination of serotype 1, in particular among individuals older than 5 years [33,52,53,58–63]. As an illustration, in The Gambia, Adegbola et al. [61] reported that serotype 1 was responsible for 20% of IPD cases in persons of all age, but 4% in infants <1 year, 17% in the 1–4 year group, 38% in the 5–14 year group, 28% in the 15–39 year group, and 23% in persons aged ≥40 years. In Burkina Faso, serotype 1 was implicated in 57% of pneumococcal meningitis cases in persons aged ≥5 years vs. 12% and 23% in persons aged <1 year and 1–4 years, respectively [53].

3.3. Pneumonia

Data on pneumococcal pneumonia are scarce, but a study from Mali revealed a higher incidence in infants <1 year (43.0/100,000), compared to 5–15 year-olds (2.5/100,000), but the CFR was as twice as high in the older (20%) than in the younger age group (10.5%) [35]. In the Gambia, during the pre-PCV13 period, the incidence of pneumococcal pneumonia was 290/100,000 in infants aged 2–11 months, only slightly higher than that in vaccine ineligible infants aged 12–23 months (260/100,000) [64]. In Togo, Moïsi et al. found that the older the age group, the higher the incidence of pneumococcal pneumonia [33]. Moreover, up to 46% of adult pneumonia cases in Kenya were estimated to be caused by *S. pneumoniae* [65], pointing to the potential substantial benefits of pneumococcal vaccines in this segment of the African population.

Overall, carriage rates are high among infants and older children, likely driving transmission to adults. The morbidity and mortality of pneumococcal disease is also borne by older children and adults, besides infants.

4. Implementation of pneumococcal conjugate vaccines in the African meningitis belt

All 26 countries of the AMB are eligible for Gavi support, including for PCV introduction. The first countries in the region to introduce PCV were Rwanda and The Gambia in 2009, followed by 19 other countries between 2011 and 2014. The last countries to introduce PCV were Guinea Bissau and Eritrea in June and August 2015, respectively. As of December 2020, the only AMB countries that have yet to introduce PCV are Chad, Guinea, and South Sudan [66].

All countries but Kenya introduced PCV without nationwide catchup campaigns. Yet, in its 2012 position paper [40], SAGE stated that 'catch-up vaccination as part of introduction will accelerate herd protection and therefore the PCV impact on disease and carriage,' and advised the administration of two catchup doses at least 2 months apart for children aged under 5 years. In the updated 2019 paper [67], SAGE reiterated that 'wherever possible, catch-up vaccination at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality.'

Moreover, all countries adopted a '3 + 0' PCV schedule, meaning a series of three primary doses given concomitantly with pentavalent (diphtheria–whole cell pertussis–tetanus–hepatitis B–H influenzae type b) vaccine at 6, 10, and 14 weeks of age, although SAGE [40] also recommended the alternative '2 + 1' schedule (2 primary doses plus a booster dose between 9 and 15 months of age), depending on countries' programmatic and epidemiologic realities, such as the burden of pneumococcal disease in early childhood.

Due to the coadministration of PCV with pentavalent vaccine, in many AMB countries, the uptake reached programmatic objectives fairly quickly. For instance, in The Gambia where

PCV13 replaced PCV7 in 2009 [43], coverage with 3 doses was 95% in 2011 [68]; in Ghana (introduction in 2012), coverage with 3 doses was 99% in 2014 [69]; in Burkina Faso and Senegal (introduction in 2013), coverage with 3 doses was 91% [70] and 89% [71], respectively, in 2014. In Niger and Togo (introduction in 2014), coverage with 3 doses was 76% [72] and 82% [73], respectively, in 2016. In Nigeria and Ethiopia, however, coverage remained suboptimal even up to 5 years following vaccine introduction, at the level of 57% [74] and 60% [75], respectively.

5. How effective is pneumococcal vaccine implementation in the AMB?

5.1. Direct effects of PCV in the African meningitis belt

The effectiveness of PCV among vaccinated or vaccine-eligible cohorts has been reported during the first 3 years of implementation, for both carriage [43,46] and clinical disease [44,45,76–80]. For instance, 2 years after the introduction of PCV13 in Burkina Faso, there was a 76% decline in the incidence of pneumococcal meningitis due to vaccine serotypes [45]; in the Gambia, following the replacement of PCV7 by PCV13, carriage due to the six additional serotypes declined from 23.9% to 13.7% [43]. Nevertheless, vaccine serotypes are still circulating, as important residual carriage has been reported from The Gambia [81,82], Burkina Faso [46], and Ghana [83,84]. For instance, 3 years after PCV13 introduction in Burkina Faso, the carriage prevalence for VT serotypes among persons of all ages was 21.6% [46]. Likewise, high residual carriage of VT serotypes has been documented in Malawi (situated outside the AMB but with comparable level of pneumococcal transmission) among vaccinated and unvaccinated persons up to 7 years after the introduction of PCV13 with a 3-dose catchup campaign for only children <1 year [85].

5.2. Indirect effects of PCVs in the African meningitis belt

Indirect effects (herd immunity) following PCV implementation are essential for the control of pneumococcal disease. In AMB countries such as Nigeria where coverage is still suboptimal, it may be too soon to record herd immunity. However, in several other countries, after several years of PCV implementation (3 + 0 schedule with no catch-up campaign) with high coverage, currently available data suggest lack of herd immunity against both carriage and disease due to the pneumococcus. In The Gambia [44], after at least 3 years of implementation, no significant reduction in the incidence of IPD was observed in individuals aged 5 years or older, especially in those aged 5–14 years (IRR = 1.05, 95% CI: 0.37–2.99). In Ghana where a serotype 1 dominated pneumococcal meningitis outbreak occurred 3 to 4 years after the introduction of PCV13 [48], the lack of herd immunity was illustrated by the fact that up to 94% of cases were individuals aged 5 years or older, ineligible for the early childhood PCV13 vaccination; similar findings were also reported from Northern Ghana by other authors [47,86]. In neighboring Burkina Faso, national surveillance data over the first 4-year post-PCV13 indicated that three in four cases of pneumococcal meningitis were aged 5 years or older [87], too old to have been vaccinated with PCV13. A carriage study we conducted in Western Burkina Faso in 2017 (3 years following PCV introduction) showed that the prevalence of vaccine serotypes (adjusted for pneumococcal detection rate) was significantly lower among children aged <5 years (partially vaccine eligible), but not among persons aged 5 years or older (unvaccinated), when compared to data from a pre-PCV carriage survey in the same population [46].

Unlike in previous examples, substantial indirect effects have been reported 5 years following the introduction of PCV 10 in Kiliffi, Kenya, with a 2-dose catch-up campaign targeting children aged up to 5 years. There was 74% and 81% reduction of the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes in persons aged 5–14 years and ≥15 years, respectively; these effects were also documented on carriage, with 62% and 77% reductions in the prevalence of vaccine type carriage in the same age groups, respectively [88]. Likewise, pneumococcal pneumonia in adults significantly declined in Western Kenya, following PCV 10 implementation [89]. Although the sites of these two studies are not situated in the Kenyan part of AMB [90,91], findings are nonetheless relevant for other high pneumococcal transmission settings, such as AMB countries.

Pre- and post-PCV pneumococcal epidemiology raises the question of whether PCV are being implemented with the most optimal strategy in the AMB. Indeed, available data suggest that a vaccine implementation strategy based exclusively on an early childhood schedule involving no mass catch-up vaccination may be inadequate to induce sufficient herd immunity to protect all unvaccinated older children and adults; this approach is unlikely to bring pneumococcal disease under control in the near term. Alternative strategies for PCV implementation are thus warranted.

6. Conclusion

The current PCV implementation strategy in most countries of the AMB (3 primary doses for infants without a booster dose) is conferring direct protection to vaccinated individuals. Conversely, indirect protection of unvaccinated individuals thanks to herd immunity generated by childhood immunization, even when restricted to those countries with high vaccine uptake such as Burkina Faso, the Gambia, and Ghana, has yet to be observed. Pre-PCV epidemiology suggests a high transmission of the pneumococcus and an important lifetime risk for pneumococcal disease. An infant-only vaccination strategy will likely require many additional years to bring pneumococcal disease under control, if ever. We therefore advocate for alternative vaccine implementation strategies, including broader age mass vaccination campaigns in the AMB, targeting children aged up to 5 years or older, to accelerate the advent of herd immunity, and thereby possibly avert thousands of deaths due to pneumococcal disease, largely due to serotype 1. Unlike countries with more mature PCV programs, those with suboptimal coverage several years after vaccine introduction should first aim to increase coverage under current implementation strategies. Countries that have yet to introduce PCV (Chad, Guinea, and South Sudan) should

seriously consider mass vaccination campaigns right from the beginning, targeting children aged up to at least five years, as was done in Kilifi, Kenya [88].

7. Expert opinion

We propose and discuss the following potential alternative strategies to maximize PCV impact in the AMB.

7.1. Switching to booster-containing doses

In higher income countries, booster-containing PCV schedules have been successful in generating herd immunity through the elimination of vaccine-type carriage and the control of pneumococcal transmission [92,93,94–99]. For instance, within the first 2 years of PCV7 implementation ('2 + 1' schedule) with 51.5% coverage, herd immunity was observed in rural South Africa, with a 64% reduction of vaccine type carriage among unvaccinated adults [99]. In addition, in PCV9 trials in the Gambia, instances of vaccine failure vis-à-vis serotype 1 disease occurring after the first year of life in infants vaccinated following a '3 + 0' schedule were documented [100]. Drawing from these experiences, it has been suggested that countries that are already implementing PCV without a booster dose (e.g. '3 + 0' schedule) could switch to a booster-containing dosing schedule (e.g. '2 + 1' schedule) [41,100], to optimize impact. This approach has the advantage of not requiring any additional vaccine doses.

However, no country of the AMB has implemented the '2 + 1' schedule hitherto, and there is no direct evidence to suggest that such a schedule change alone will quickly yield indirect effects as was seen elsewhere; an immunogenicity study comparing the '2 + 1' to the "3 + 0" schedules in Burkinabe infants before PCV introduction could not conclude whether one schedule was superior to the other [101]. Furthermore, reducing the number of primary doses could even lead to insufficient direct protection until the booster dose is given, and thus to more deaths, during the critical early childhood period [102]. It therefore remains uncertain whether shifting the third dose toward the second year of life will yield herd immunity in the AMB.

7.2. Broader age group mass vaccination campaigns

This approach is supported by the following facts: First, broader age group mass vaccination campaigns to control pneumococcal carriage and disease is justifiable by both pre- and post-PCV introductory epidemiological data. Indeed, pre-PCV data show a substantial burden of disease and carriage among older children and adults, and post-PCV data indicate persistent vaccine serotype carriage and lack of indirect protection of unvaccinated individuals, except in Kenya where PCV was introduced in routine with a catch-up campaign. Secondly, the effectiveness of catchup campaigns in eliminating vaccine type (VT) carriage and rapidly generating herd immunity has been shown by mathematical models fitted to data from Vietnam [103] and Kenya [104]. These models showed that vaccinating all children aged <5 years with PCV at the time of PCV introduction into the routine schedule led to an accelerated impact through both direct and indirect protection.

Thirdly, mass vaccination campaigns have proven very effective in the past in dramatically reducing bacterial disease in all age groups through both direct and indirect protection, as was the case with *Haemophilus influenzae serotype b* (Hib) disease in England [105] and meningococcal meningitis in the AMB [12,14].

Fourthly, mass vaccination campaigns will provide an opportunity to vaccinate toddlers and older children, either with a priming dose, or with a booster dose, depending on their current immunization status. This may have the following advantages:

1) Insofar as these groups (but not infants) are shown to be the drivers of pneumococcal transmission [106,107,108], vaccinating them could significantly alter the circulation of the pneumococcus. As PCV was introduced in the AMB between 2009 and 2015 without nationwide catchup campaigns except in Kenya, the 1–10 year age group is partly vaccinated, with greater unvaccinated proportions in countries of recent PCV introductions. In Burkina Faso, for instance, all children born before 1 June 2013 (aged 7.5 years or older in January 2021) are unvaccinated with PCV owing to the lack of a catch-up campaign during PCV introduction in October 2013; thus, vaccinating the 1–10 year group would provide a priming dose to some children, and a booster dose to others.

2) Further, data from Australia suggest immunity in children vaccinated following a '3 + 0' schedule may wane with time [109]. In rural Gambia [82], 10 years after PCV implementation following a '3 + 0' schedule, the reduction of vaccine serotypes has plateaued, with important residual carriage in all age groups. In a systematic review by Bonner et al. [110], PCV administration after the first year of life significantly reduced both carriage and IPD.

These data suggest all birth cohorts vaccinated without a booster dose would also benefit from a broader age group mass vaccination campaign.

The main barrier to the implementation of mass vaccination campaigns is likely to be the limited financial resources. Nevertheless, the availability of new PCVs, with the prequalification of a recent PCV10 that is 43% cheaper than current vaccines obtained through Gavi [111,112], and implementation strategies prioritizing integration with other vaccines to minimize operational costs could bring PCV mass vaccination campaigns within reach for low-income countries such as those of the AMB.

On the way forward, more formal evidence from both empirical and modeling studies is needed to inform countries on whether their specific situation warrants mass vaccination campaigns, and if so, what implementation scenarios would be the most cost-effective.

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Declaration of interest

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Author contributions

LK and AG conceived the idea and the approach for the manuscript. LK and ARS wrote the initial draft of the manuscript, which was reviewed by AG and AGL. LK coordinated the finalization of the manuscript. The final version was reviewed and approved by all authors.

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8. Conclusion and perspectives

8.1. Summary of evidence

8.1.1. Immunization data-related challenges and implications for vaccine impact assessment

We explored the issue of immunization data recording in Burkina Faso through the conduct of a cross-sectional survey in 30 health facilities to assess some characteristics and the completion (filling) of vaccination home-(HBR) and facility-based records (FBR); these forms are critical sources of individual vaccination information.

The assessment found a range of shortfalls, including the lack of standardization of these recording forms across health facilities and study participants (half of HBRs and a third of FBRs were outdated), and their inconsistent or untimely filling by vaccinators (vaccines may be administered but recording is overlooked or postponed to a later date). These issues resulted in discordant individual vaccination status or vaccine coverage estimates between HBRs and FBRs, as illustrated by the moderate agreement (median of 0.48) between these two sources of information; coverage estimates based on either document were sensitive to the addition of information obtained from caregivers' recall.

These recording challenges were reflected in the separate and unrelated study on pneumococcal carriage. Indeed, PCV vaccination status of some vaccine-eligible children could not be ascertained due to the absence of written proof of vaccination; for instance, among participants aged 12-23 months, 6.1% and 26.6% had unknown PCV status in 2015 and 2017, respectively (see article 3). Such difficulties in ascertaining individual vaccination status in the routine immunization schedule will constrain and limit vaccine impact studies. In the absence of sophisticated research platforms where rigorous vaccine exposure and disease status can be maintained, head-to-head comparisons to derive vaccine effectiveness will be threatened by information bias as a result of misclassification, if doable at all.

Given that data-related challenges will require time and resources to address, alternative approaches may be the only options to assess vaccine impact in this setting. For the pneumonia (article 2) and carriage (article 3) studies, we used an ecological approach where vaccine-eligible groups (potentially vaccinated) were compared to vaccine-ineligible groups (not vaccinated). In article 2, we developed an interrupted time-series modelling where the main predictor was time period vis-à-vis PCV introduction in Burkina Faso: all time points before vaccine introduction were considered "unvaccinated", and all time points post-introduction were considered "vaccinated", while allowing for a 12-month vaccine deployment transition phase. Similarly, in article 3, we compared carriage rates before (using historical data obtained from a 2008 survey) and after PCV introduction (using data from surveys conducted in 2015 and 2017). Acknowledging the limitations of ecological comparisons in epidemiologic research [74], we attempted to minimize bias by making groups as comparable as possible through the harmonization of case definitions, study sites, laboratory methods, and investigators/data collectors.

8.1.2. PCV impact on pneumococcal carriage and disease

Nearly three years following PCV13 introduction in Burkina Faso's routine infant immunization program, we documented significant reductions in the percent of pneumococcal carriers with a vaccine serotype (VT) among children aged < 5 years (partially vaccinated). Indeed, compared with the pre-PCV period, we observed reductions of 34% and 42% among children aged <1 year and 1-4 years, respectively. Nevertheless, VT carriage remained common, with rates of one third and one fifth among children < 5 years and all participants (children and adults), respectively. Among participants ≥5 years of age, the proportion of pneumococcal carriers with a VT did not change significantly after PCV introduction, indicating a lack of herd immunity and an uncontrolled community transmission of VT pneumococci (article 3).

The direct effects of PCV on carriage among children aged < 5 years was translated into reductions in all-cause pneumonia hospitalizations (article 2). The vaccine was associated with significant reductions in the rates of pneumonia hospitalization (-34%) and pneumonia-related deaths (-51%). No reduction was observed in the rates of control condition (severe acute malnutrition and unintentional injury), lending support to study internal validity. As this study did not include data on individuals aged ≥ 5 years, we cannot tell if PCV13 introduction generated herd immunity against pneumonia. However, this is unlikely to have occurred, given the absence of evidence of herd immunity against pneumococcal carriage, which usually precedes clinical disease.

The absence of herd immunity is further supported by the findings of our review on the impact of PCVs in the African meningitis belt region (article 4), with data on invasive pneumococcal disease (including pneumococcal meningitis) from The Gambia [(50)] and Ghana[(11)]. A study in Burkina Faso[(73)] found significant reductions of VT pneumococcal meningitis in all age groups (thereby suggesting the existence of herd immunity), but the concurrent declines of non-vaccine serotypes (NVT) pneumococcal meningitis indicates serious bias cannot be ruled out, especially given the absence of herd immunity against carriage in our study (article 3).

8.2. Policy implications of the findings

8.2.1. Immunization data-related challenges

Given the implications of inadequate recording practices on the estimation of vaccine uptake and impact, there is a pressing need to address the gaps identified. In the short term, the Ministry of Health in concertation with its partners can implement the following corrective measures, as most of them can be integrated into already existing and funded activities to save costs: ensure relevant actions are taken into considerations in strategic and annual planning; redesigning regularly and pretesting HBRs and FBRs to ensure alignment with the evolving routine immunization schedule; ensuring an uninterrupted procurement of these tools; and strengthening the capacity of health workers through training, supportive supervision and implementation of job-aids.

In the mid-to-long term, the country may consider the implementation of an electronic immunization registry (EIR). Although not a panacea for poor data quality, experiences from elsewhere [(75-77)] indicate that EIR can help optimize service delivery with useful functionalities

such as tracking child vaccination records from multiple immunization facilities, and reminder of overdue vaccines.

8.2.2. PCV impact on pneumococcal carriage and disease

Both carriage and pneumonia studies show evidence of direct effects of PCV in Burkina Faso. These findings are expected and in line with previous studies both in LMICs [49,53-54,78] and HICs [48,51,79]. The use of PCV13 or other pneumococcal vaccines should be sustained by the Ministry of health as a key strategy to reduce the burden of pneumococcal disease.

As indirect effects through herd immunity have yet to be observed, alternative implementation strategies of PCV13 may be the way forward. Indeed, PCV13 was introduced in Burkina Faso without a catch-up campaign, based on 3 primary doses administered between two and four months. In fact, all Gavi-eligible countries in Africa but Kenya introduced PCVs following the same pattern [37]. Post-PCV epidemiological data from Burkina Faso, the Gambia and Ghana, all of which introduced PCV without a catchup campaign, when compared with data from Kenya, show the value of catchup campaign in the rapid generation of herd immunity. The current PCV implementation strategy may not be the most optimal for AMB countries such as Burkina Faso where the epidemiology of the pneumococcus is specific, characterized by a considerable lifetime risk of infection and the dominance of serotype 1 in pneumococcal meningitis.

Altogether, our findings support the adoption of broader age group mass vaccination campaigns in addition to the routine implementation of PCV, targeting older children, to accelerate the onset of herd immunity in the country.

8.3. Limitations and suggestions for future studies

8.3.1. Immunization data-related challenges

The assessment of vaccination recording tools has been conducted in 10 low-performing health districts which were targeted by an immunization strengthening intervention in the context of the Global Health Security Agenda (GHSA). Therefore, the results may not reflect the true situation in the rest of the country. Further limitations to be accounted for in future studies include the non-probabilistic sampling used to select health facilities and participants, not taking pictures of HBRs systematically, and verifying only the presence of recording fields for recommended vaccines while other characteristics could have been examined. Indeed, as per WHO's guidance[80], a broader set of elements should be considered when designing a HBR, including the following: data recording field for the date of next vaccination; form version control information; space for vaccines administered outside the routine immunization schedule; font type and size; space for health worker's signature; flexible layout to account for changing schedules; the national immunization schedule and recommended age for the administration of each vaccine dose; quality of the material used to print the HBR (e.g thickness of the paper); and size, format, and color of the HBR.

Besides addressing the abovementioned limitations, future research on recording forms should explore the following aspects:

- Patterns and determinants of the retention of HBRs by caregivers

Many household surveys including cluster sampling vaccine coverage survey[81], demographic and health surveys[82] and multiple indicator cluster survey [83] rely on HBRs to obtain information on vaccines received by survey respondents. How long HBRs are kept in households and what factors influence retention are interesting and open research questions.

- Efficiency of adding FBRs as source of vaccination information during surveys

HBRs and FBRs should provide the same information with regard to the immunization status of a given child. In the absence of HBR, surveyors may resort to FBR to collect the needed information. This, however, poses logistical challenges, as field teams need to report to the health facilities where vaccines have been administered to retrieve missing data, which will require additional time and resources. Although the process may increase the sensitivity of the assessment by some percent points, a useful research question is whether these gains are worth the additional efforts.

8.3.2. PCV impact on pneumococcal carriage and disease

Our assessment of the impact of PCV13 in Burkina Faso on both carriage and pneumonia-related hospitalizations was conducted during the first 5 years following introduction. Thus, the data generated are only about the early effects of the vaccine. Yet, the comprehensive appraisal of the long-term public health impact of PCV13 requires a continuous monitoring through surveillance and special epidemiological and clinical studies on various outcomes. Further studies are therefore needed to gather evidence on the following topics:

- Herd immunity

The superiority of conjugate vaccines over polysaccharide vaccines in preventing bacterial diseases lies in the ability of the former to alter transmission dynamics through protection against asymptomatic carriage, which ultimately leads to the protection of unvaccinated persons against disease (indirect effects or herd immunity) [53,84]. Additional studies are needed to document indirect protection of PCV13 against pneumonia and meningitis among unvaccinated individuals in Burkina Faso.

- Serotype replacement (carriage, disease)

The benefits gained through the direct and indirect effects of PCVs can potentially be offset by the phenomenon of serotype replacement whereby serotypes not included in the vaccine emerge and replace vaccine serotypes in both carriage and disease [56,57] We did not specifically assess serotype replacement and cannot rule it out in Burkina Faso. Continuous surveillance and research activities should aim at documenting the existence and magnitude of serotype replacement.

- Cost-effectiveness

Beyond evidence on the reduction of the burden of pneumococcal disease, cost-effectiveness analyses which compare health outcomes with the costs of PCV vaccination programs are useful to decision-makers. As Ministries of health are more and more confronted with difficult choices as to where scarce resources should be allocated or which disease prevention approach should be prioritized, value for money analyzes will provide evidence base for decision and resource mobilization. Such analyzes can not only compare different

pneumococcal vaccines (including higher valency vaccines under development), but also alternative implementation strategies (e.g the role of catchup campaigns).

Although the cost-effectiveness of PCVs have been established in many settings, we are not aware of any published study addressing this question in the specific context of Burkina Faso.

- Optimal implementation strategies

Country-specific evidence is needed to decide on the best dosing schedule (e.g value of a booster dose) and on the potential impact of mass vaccination. Mathematical modelling studies have shown the value of catchup campaigns in the quick elimination of pneumococcal carriage and disease in Vietnam [(85)] and Kenya [(86)]. The same models could be parametrized with data from Burkina Faso to draw meaningful conclusions.

- Antimicrobial resistance

Studies have documented declines in the incidence of pneumococci resistant to antimicrobials following the introduction of PCV [(87)]. This is an additional and unintended benefit of PCVs, adding potentially to their cost-effectiveness. Longitudinal studies could assess the same outcomes in the context of Burkina Faso. Alternatively, useful conclusions could be drawn by analyzing data from the disease surveillance department of the Ministry of Health or pneumococcal reference laboratories collected over several years.

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