Evaluation of Environmental and Immunization Interventions in Shaping Respiratory Health in Low and Middle-Income Countries

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B.S. in Biology and Society, May 2014, Cornell University
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A Dissertation submitted to

The Faculty of
The Milken Institute School of Public Health
of The George Washington University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

May 17, 2026

Dissertation directed by

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Dedication

I dedicate this dissertation to my beloved family, whose unwavering support carried me through this PhD journey. This has been a long and demanding path, and without their endless love and encouragement, I would not have been able to earn this degree, grow professionally, or engage in the research that has shaped my time at GWU.

I owe so much of who I am today to my mother, Dr. Sorim Hwang. I still vividly remember her years at Ewha University, commuting over two hours each day while studying, caring for her family, and raising two young children. Despite these challenges, she graduated in just four years. Yet, after achieving that milestone, she made the difficult decision to set aside her own career, even turning down an opportunity from a prestigious institution, in order to dedicate herself fully to her family. This dissertation, and this degree, exist because of her sacrifices. Thank you, 엄마, for everything. I love you so much.

I also want to honor my dear grandfather, who generously supported my education abroad. He passed away in 2025, and I was unable to attend his funeral—something I will always carry with me. He believed in me wholeheartedly, driven by his deep love for his grandchildren and his unwavering faith in the power of education. Beyond financial support, he gave me wisdom, life lessons, and stories of his own journey, always hoping we would carry forward his humility and diligence. 할아버지, I promise to use this degree to do meaningful work that helps others and contributes to our world. I miss you deeply.

I am also profoundly grateful to my father. Before and after marriage, he carried the responsibility of supporting his family with dedication and strength. As a physician, he has always cared for his patients with compassion and integrity, serving as a constant source of inspiration to me. Despite his demanding schedule, he always made time to check in on me, encourage me, and ensure my well-being. I am incredibly proud to be his daughter and grateful to be part of this family.

Finally, to my husband, Dr. Brian Wu—thank you for standing by me through everything. Thank you for loving me unconditionally, for your patience, and for always believing in me, even when I struggled to believe in myself. You have been my constant source of strength and comfort. I love you so much, and I look forward to building our future together.

I cannot thank enough all the people who have been part of this journey. I carry with me the support, sacrifices, and love of so many individuals who have shaped my path. I will make sure that this degree does not go to waste. This achievement is not mine alone—it belongs to everyone who stood by me along the way. 감사합니다.

Acknowledgements

I would like to take a moment to sincerely thank my dissertation committee members, Dr. Emily R. Smith, Dr. James Tielsch, and Dr. Joanne Katz. Dr. Smith, I am deeply grateful for your invaluable guidance and mentorship throughout this process. Your thoughtful feedback and critical insights have played a fundamental role in shaping me into a more rigorous and thoughtful researcher. Dr. Tielsch and Dr. Katz, thank you for your continued involvement and support, and especially for the generous opportunity to work with such valuable trial data. Through this work, I have learned immensely and grown into a more competent and confident researcher.

I would also like to express my sincere gratitude to other faculty members who have supported me along this journey. Dr. Adrienne N. Poon, thank you for providing meaningful research opportunities through our work on Asian health disparities and COVID-19. As an Asian American researcher, it has been especially meaningful to work alongside someone whose work is deeply driven by a commitment to serving communities in need. Your dedication continues to inspire me. Dr. Mimi Ghosh, thank you for the opportunity to collaborate on the COVID-19 study, and for the inspiring class that first connected us. I am grateful that we were able to reconnect through research, and I deeply appreciate your mentorship and guidance.

Dr. Anne Monroe and Dr. Amanda Castel, thank you for the opportunity to be involved in the DC Cohort study. I truly appreciate your willingness to include me and support my development, even without a formal position. Beyond the research

experience, I am grateful for the values I have learned from you about what it means to be a thoughtful and impactful investigator.

Lastly, I would like to thank my manager and AVP at Merck, Susanne and Kai-Li. Thank you for the opportunity to be part of your team during my PhD. I am deeply grateful for the insights I gained from working with you in an industry setting, which broadened my perspective and opened my eyes to another side of healthcare. I also sincerely appreciate your continued support and the effort you made to keep me on the team despite the challenges associated with my international status.

Most importantly, I want to thank all of you for your support in helping me reach this next stage of my career. Your encouragement during my transition, and for some of you, your support during my immigration challenges, meant more than I can fully express. As an international student, it has been incredibly reassuring and meaningful to have such a strong network of faculty support during times of uncertainty. I am truly grateful.

Abstract of Dissertation

Evaluation of Environmental and Immunization Interventions in Shaping Respiratory Health in Low and Middle-Income Countries

From development through adulthood, respiratory health is shaped by a complex interplay of socioeconomic, biological, environmental, and cultural factors across the life course. While numerous interventions target these domains to improve respiratory outcomes, it is essential to rigorously assess their effectiveness and determine how they can be integrated into broader public health strategies. This dissertation focuses on the roles of environmental and immunization interventions in shaping respiratory health among populations in low- and middle-income countries (LMICs). The first two papers draw on data from the Nepal Cookstove Intervention Project, a pair of randomized trials conducted in rural Nepal between 2010 and 2014. These trials aimed to evaluate the impact of clean cooking interventions on air quality, reproductive outcomes, and respiratory morbidity among young children. In the first paper, we examined whether clean cooking reduces respiratory infections and whether different stove technologies differ in their effectiveness. Although cleaner cookstoves substantially reduced air pollution compared to traditional stoves, their impact on respiratory infections was modest, with no meaningful differences observed between stove types. Notably, greater benefits were observed among households with smokers and those that installed stoves during winter. These findings suggest that while clean cooking has measurable benefits, maximizing its impact requires addressing additional pollution sources and improving sustained use and compliance. In the second paper, we evaluated the effect of clean cooking on pulmonary function. We found that clean cooking was associated with

improved lung function, including a significant reduction in the risk of pulmonary obstruction. The magnitude of benefit varied by household context, with stronger effects observed in households with smokers and those using outdoor installations. These results highlight that ventilation and continued exposure to pollutants remain critical factors influencing intervention effectiveness. The third paper utilized Demographic and Health Surveys and Multiple Indicator Cluster Surveys to assess the broader population-level impact of pneumococcal conjugate vaccine (PCV) on acute respiratory infection (ARI), antibiotic use during ARI episodes, and under-five mortality. We found that both PCV introduction and increasing coverage were associated with reductions in ARI prevalence. However, no significant reductions were observed in antibiotic use or under-five mortality. These findings suggest that while PCV plays an important role in reducing respiratory disease burden, maximizing its impact requires complementary strategies, including improved antibiotic stewardship and adherence to clinical guidelines. Overall, this dissertation demonstrates that while environmental and immunization interventions can yield meaningful improvements in respiratory health, their effectiveness is influenced by contextual and behavioral factors that are difficult to control in real-world settings. These findings underscore the importance of considering implementation context, strengthening intervention adherence, and integrating other community-based strategies. Future research should evaluate these interventions across diverse populations, longer time horizons, and varied methodological approaches to generate more consistent and generalizable evidence. At the same time, the results presented here provide important insights to inform policy and guide the design of more effective public health interventions.

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Chapter 1. Introduction

1.1 Background

Respiratory health plays a central role in human wellbeing and is shaped by a wide range of biological, environmental, and social factors throughout the life course. Respiratory illness remains a major contributor to global morbidity and mortality, affecting populations across diverse geographic and socioeconomic contexts. This burden also reflects the combined influence of host characteristics, living conditions, and access to preventive and health care resources. Because these factors interact in complex ways, understanding the determinants of respiratory health requires considering both individual-level biological processes and broader structural conditions that influence exposure, susceptibility, and protection. Such a perspective is particularly important when examining how different interventions and environmental conditions shape respiratory outcomes across populations.

Early-stage immune system and susceptibility

One important period in shaping respiratory health occurs during early life, when key physiological systems are still developing. Infancy and childhood are critical periods for the development of the immune system and vital organs. During maturation, innate immunity plays a more prominent role than adaptive immunity, which has had limited antigen exposure. (1) Newborns receive maternal antibodies through transplacental transfer before birth although these antibodies are present in finite amounts and decline over time. (1, 2) At the same time, several aspects of neonatal immune function remain underdeveloped, including reduced secretion of bioactive molecules, lower expression of co-receptors, and diminished cytokine responses and phagocytic activity, all of which

contribute to weaker responses to pathogens compared with later stages of life. (3-5)

As children grow, repeated exposure stimulates antigen recognition and the development of immunological memory that can persist throughout the lifespan. (1) Lung development also begins early in gestation and continues through adolescence and young adulthood. Although neonatal lungs are capable of gas exchange at birth, they remain structurally immature and undergo ongoing development of alveoli, secondary crests, and pulmonary microvasculature. (6) Pulmonary function increases with age and height during childhood and follows a more complex growth pattern during adolescence, continuing to rise even after adult height is reached as respiratory muscle strength develops. (7)

The role of vaccines and access to vaccination

Yet, respiratory health is also shaped by the environment and physical resources besides the immunological and physiological factors standalone. Immunization, for example, has been a key player in eliciting antibodies against a specific pathogen that otherwise develop through a natural infection. When administered, vaccines trigger the production and maturation of memory B cells that secrete antibodies against the target pathogen, which remain alive after the pathogen clearance. Upon re-exposure to the same agent, the memory recall response will be more specific and stronger than a naïve response. (8) The recent COVID-19 pandemic was a great representation of the human need for additional immunological protection beside the natural immunity in our system, where the vaccination prevented approximately 19.8 million (95% CI 19.1-20.4) deaths from COVID-19 in 185 countries and territories (9) and was associated with a reduced

risk of hospitalization and severe COVID-19 outcomes such as acute respiratory distress syndrome and progression to invasive mechanical ventilation. (10-12) Other vaccine-preventable diseases (VPD) also show the added benefits of vaccines. For example, measles, an airborne viral disease caused by morbillivirus that is highly contagious and may cause serious health complications among children younger than 5 years old, was successfully prevented by the introduction of vaccines, preventing 23.2 million deaths between 2000 and 2018. (13, 14) A recent modeling study by WHO reveals that since 1974, vaccination has averted 154 million deaths, among which 146 million were among children under 5 years old. This equates to 9 billion life-years saved and 10.2 billion healthy years gained after accounting for the added benefit of reduced morbidity. (15)

Vaccine accessibility, however, is also dependent on each country's policies, health and financial resources, and various individual cultural and socioeconomic factors. In particular, issues regarding vaccine accessibility are reported to be prevalent in low- and middle-income countries (LMICs) and rural areas in some high-income countries, where manufacturing and storage capabilities, distribution logistics, and other associated operating costs, such as those for raw materials, skilled personnel, utilities, as well as the lack of specific expertise and technical support, can be major barriers. (16-18) Besides the challenges within the vaccine manufacturing and distribution pipeline, a country's political prioritization, disease burden, and the availability of human resources and surveillance systems are additional factors impeding nationwide immunization. (19)

Thus, LMICs have relied mostly on vaccine donations from high-income countries and support from international organizations including Gavi. (20, 21) Nonetheless, vaccination rates have proceeded at very different rates across countries'

different demographic groups. For example, children from low-income families and rural households are less likely to be fully immunized due to vaccine affordability, distance to healthcare facilities, and parental awareness. (22, 23) Vaccine hesitancy, low trust, and cultural beliefs also contribute to the impediment to successful immunization. (24, 25) Overall, the successful implementation of immunization programs in a country requires a comprehensive approach that addresses financial, logistical, and socio-cultural barriers.

Air pollution

The environment, especially air quality, is also deeply intertwined with our respiratory health. It is well-established that air pollution induces worse health outcomes. Specifically, particulate matter (PM), a mixture of solid particles and droplets in the air that is 10 microns or less in diameter (PM_{10}), is inhalable into the lungs, which also induces adverse health outcomes. Fine particulate matter, known as $PM_{2.5}$, that is 2.5 microns or less in diameter, is also inhalable but also may enter our bloodstream through the lungs. (26, 27) These particulate matters are from various but different emission sources. According to the California Air Resources Board, $PM_{2.5}$ pollution is mainly emitted from the combustion of gasoline, oil, diesel fuel, or wood, or indoor activities such as smoking tobacco and cooking, along with a significant portion of PM_{10}, whereas PM_{10} can also come from dust from construction sites, landfills, wildfires, and other industrial sources. (28) Exposures to particulate matters have been associated with increased risks of multisystem morbidities, including asthma, lung cancer, acute and chronic bronchitis, chronic obstructive pulmonary disease, as well as reduced lung function growth among children. (26-28) The most vulnerable groups to air pollution include older adults with chronic heart or lung disease, and young children as they inhale

more air per pound of body weight due to faster breathing relative to their smaller body sizes and immature immune systems. (28-31) According to the State of Global Air, 6.67 million deaths worldwide were attributable to air pollution in 2019 (32) , and a systematic analysis for the Global Burden of Disease Study 2019 showed the ambient $PM_{2.5}$-attributable burden had changed from the 13th leading risk in 1990 to the 7th in 2019 for all ages. (33)

The distribution and health damages of air pollution also vary by location and socioeconomic group, with growing evidence suggesting a disproportionate burden of air pollution among people living in LMICs or low-income groups, compared to those living in developed countries or higher socioeconomic status. (34-36) Rentschler and Leonova. (2023) report that 7.3 billion people are directly exposed to unsafe levels of PM2.5 concentrations annually, 80% of whom live in LMICs. (34) Several factors contribute to this unequal burden across populations, including heavier dependence on polluting industries and technologies, cut-and-burn agricultural practices, and heavy use of biomass fuels for cooking and heating. (36) Households in LMICs, especially those that live in low quality housing, particularly suffer from greater exposure to household air pollution (HAP), where cooking is conventionally done in poorly ventilated spaces with inefficient combustion devices that emit high levels of air pollutants including particulate matter. (37) Moreover, the health damages associated with indoor air pollution can be substantial because pollutant concentrations inside households are often 2–5 times higher than outdoor levels. As a result, individuals living in homes without adequate ventilation or access to open spaces, particularly those with enclosed indoor kitchens, may experience greater exposure and consequently face a higher risk of respiratory morbidity. (38, 39)

1.2 Research Aims

Consequently, our respiratory health results from the interplay of immunological, physiological, environmental, and socio-economic factors. Understanding these elements is crucial for effectively protecting respiratory health. Continued research is necessary to explore their complex interactions to provide the basis for addressing their impacts and developing public health initiatives. Enhanced efforts in research will allow us to devise comprehensive strategies that address the multifaceted nature of respiratory health, ensuring better outcomes for diverse populations. Thus, this dissertation aims to answer the questions regarding these factors. The dissertation has three aims:

Aim 1. To evaluate the effect of clean cooking interventions on respiratory morbidity among children younger than 36 months and compare respiratory outcomes across different clean cooking technologies, and to assess whether these effects differ across population subgroups

Aim 2. To assess the effect of clean cooking on lung function among individuals 10 years or older and assess the intervention effect by different population subgroups

Aim 3. To assess the population-level impact of pneumococcal conjugate vaccine in reducing acute respiratory infection (ARI) and antibiotic consumption during the episodes of ARI among children living in LMIC

Chapter 2. Assessing the Impact of Improved Biomass and Liquid Petroleum Gas Stoves on Respiratory Illness in Young Children: Findings from Two Randomized Community-Based Trials in Rural Nepal

Abstract

Background

Solid fuel combustion generates pollution that heightens children's risk of respiratory illness. In Nepal, open-fire cooking is common, making household air pollution a major contributor to child morbidity. This study evaluated the impact of clean cooking on respiratory outcomes in young children.

Methods

The Nepal Cookstove Intervention Project (2010-2014) comprised two randomized trials: Trial 1 comparing traditional and Envirofit stoves, and Trial 2 comparing Envirofit and LPG stoves. The primary analysis included children under 36 months, with acute lower respiratory infection (ALRI), acute respiratory infection (ARI) and influenza-like illness (ILI) as outcomes. Relative risks were estimated using modified Poisson mixed-effects models, with effect modification by demographic and household factors assessed using Wald tests.

Results

A total of 4,748 children were randomized to Envirofit in Trial 1, and 1,404 children were randomized to the Envirofit group and 1,464 to the LPG group in Trial 2. In Trial 1, ALRI, ARI, and ILI incidence declined, with non-significant risk reductions of 11.6%, 8.6%, and 10.5%, respectively. In Trial 2, LPG non-significantly reduced ALRI by 25.8%, ARI by 16.7%, and ILI by 4.6% compared with Envirofit. In Trial 1, ILI risk was lowest among households receiving winter installations. In Trial 2, households with

smokers experienced the greatest benefit from LPG stoves, with lower ARI and ILI risk compared to Envirofit cohort. PM concentrations declined after Envirofit installation in Trial 1 and were lower in LPG households in Trial 2.

Conclusions

Clean cookstoves lowered PM levels but provided only modest respiratory benefits, likely limited by high residual exposure that remained above World Health Organization (WHO)-recommended exposure thresholds and continued use of non-intervention stoves. Future studies should assess long-term health impacts and incorporate biomarker data to clarify the respiratory effects of clean cooking

2.1 Introduction

Early childhood is a period of heightened susceptibility to a wide range of infections, driven by underdeveloped immune system. (40, 41) This vulnerability is further compounded by environmental and sociodemographic factors which influence both the risk and progression of disease. (42-44) Among the various causes of disease burden in children under five, acute respiratory infections (ARIs) are the leading cause of children's morbidity and mortality worldwide (45-47), which are a group of infections affecting the either upper or lower respiratory tract. (48) The upper respiratory tract infections (URTIs) include conditions such as rhinitis, sinusitis, pharyngitis, while the lower respiratory tract infections (LRTIs) including pneumonia, bronchiolitis, tracheitis, and others. (48)

Globally, ARIs account for an estimated 12 million hospital admissions and 1.3 million deaths annually in children under five. (49, 50) In 2021, URIs contributed to 12.8 billion episodes and 19,600 deaths worldwide, with the highest burden occurring in neonatal and pediatric age populations. (51) The global age-standardized incidence rate for LRTIs was 4283.61 per 100,000 population (95 % UI: 4057.03 per 100,000, 4524.89 per 100,000), with the most severe impacts reported in South Asia, southern sub-Saharan Africa, and western sub-Saharan Africa. (51) One major driver of this burden is energy poverty, wherein many households rely on traditional cooking using unclean solid fuels for heating, lighting, and cooking. The use of solid fuels generates harmful pollutants that pose a significant threat to respiratory health. Fine particulate matter (PM), released during the combustion of these fuels, can penetrate deep into the lungs and damage the alveolar lungs. (52) Studies suggest the exposure to PM induces oxidative stress and

triggers inflammatory signaling pathways, ultimately impairing airway immune function and increasing susceptibility to respiratory infections. (53, 54) Additionally, PM pollution can exacerbate pre-existing respiratory conditions such as asthma and allergies, and the associated inflammatory responses may heighten the risk of adverse outcomes when individuals with these conditions are affected by acute respiratory infections (55-57).

According to the 2023 International Energy Agency (IEA) report, approximately 2.3 billion people still utilize biomass stoves. (58) In Asia alone, about 1.46 billion people were reported to rely on open-fire cooking. (58) For instance, in 2018, only 28% of households in Nepal had access to clean cooking facilities, compared to a global average of 59%. (59) In Bangladesh, nearly 80% of households were reported to rely on solid fuels in 2022 (60) while in India, the National Family Health Survey 2019-2021 reported that approximately 24.1% of the households had no separate kitchen for cooking or cooking area that was properly ventilated. (61) The associations between ARI and air pollution have been well established where traditional cooking method is predominant. For example, a retrospective cohort study of young children living in India reported that each 10$\mu g/m^3$ increase in $PM_{2.5}$ was associated with 23% higher odds of ARI, and children exposed to the highest quartile of $PM_{2.5}$ exposure had over four times the odds of ARI compared to those exposed to the lowest quartile. (55) Similarly, a 2019 cross-sectional study in the city of Bamenda, Cameroon showed the participants who were exposed to indoor cooking and open fire cooking were 3.62 times and 1.91 times more likely to develop ARI compared to those who were unexposed to cooking smoke. (62) Another cross-sectional study in Nepal at Kathmandu valley showed that out of 286 children, 60.8% of study population had ARIs, and nearly 20% of children had severe or

very severe pneumonia, where the cooking fuel exposure inside the kitchen was identified as a significant risk of contracting ARI. (63)

Several modifiable factors, such as socioeconomic status, sex, season, and birthweight, can influence the risk of ARIs associated with household air pollution (HAP)In many low and middle-income countries (LMICs), women, especially those residing in rural areas, are bound to cultural norms carrying out domestic tasks such as cooking, often coupled with the use of open hearths. As a result, women experience extended exposure to kitchen smoke, and the close presence of young children amplifies their joint risk of ARIs. (64-66) Households of lower socioeconomic status (SES) are also more likely to depend on solid fuels due to the high cost and limited accessibility of cleaner cooking alternatives. (67, 68) Seasonal variation also influences exposure levels. During winter, reduced wind speeds and higher humidity limit pollutant dispersion, leading to elevated indoor concentrations compared to warmer months, joined with increased time spent indoors that heightens exposure to HAP from cooking and heating. (69-71) Moreover, low birth weight (LBW) infants, born with underdeveloped lungs and weaker respiratory muscles, are highly prone to respiratory infections. (72, 73) HAP has also been associated with an elevated risk of LBW and further exacerbates the vulnerability of these infants by impairing respiratory immune defenses, creating a complex cycle of heightened risk. (72, 73)

Clean cooking has become a key priority in global development and was formally incorporated into the United Nations Sustainable Development Goals (SDG 7) in 2015. (74) Despite ongoing global efforts, the transition to clean cooking has progressed slowly— between 2010 and 2021, access to clean cooking technologies increased by only

1.4% annually(75). Despite a growing body of literature on clean cooking, evidence on the health benefits of improved cookstoves remains mixed and limited, with some studies demonstrating significant benefits while others report non-significant effects. (76-80) Notably, there is a lack of experimental studies directly linking clean cookstove use to reductions in acute respiratory infections among young children in South Asia. (81) Furthermore, the health impacts of domestic energy poverty on children remain understudied compared to other vulnerable groups, such as the elderly. (82) The role of population and household characteristics as potential effect modifiers of cookstove efficacy also has also not been thoroughly examined.

Understanding the health impacts of cleaner cooking interventions is essential, particularly among young children who are susceptible to the adverse effects of household air pollution. Although previous evidence links exposure to biomass smoke with increased respiratory morbidity, few randomized studies have rigorously assessed the effectiveness of alternative cookstoves in reducing respiratory outcomes in children. To address this gap, the present study aims to assess the effect of alternative cookstoves on respiratory morbidity among children younger than 36 months old. We also aim to evaluate effect modification by age, sex, smoker presence, season of cookstove installation, birth weight, cookstove location, and chimney installation. In this study, we adopt additional and slightly different approaches compared to the previously published work by Tieslch et al (2016). (83) Also, given that ARI encompasses a broader spectrum of respiratory infections as defined by World Health Organization (WHO) and United Nations Children's Fund (UNICEF) (84), we included ARI as our additional primary outcome. Furthermore, we incorporated data from the Trial 2 to introduce an effect

comparison by stove type.

2.2 Methods

Study population

The Nepal Cookstove Intervention Project (NCT00786877) comprised a pair of randomized trials designed to evaluate the impact of cleaner, alternative cookstoves on indoor air quality, respiratory morbidity in children, and reproductive outcomes among population residing in the Sarlahi District in the Terai region of southern Nepal. The Terai, a low-lying floodplain of the Ganges River, is densely populated and predominantly rural. (85, 86) Most residents engage in farming or labor-intensive work, and literacy levels remain low, particularly among women. (86) According to the 2021 national census, approximately 40% of the population in Sarlahi District reported being unable to read or write, with females accounting for about 60% of this illiterate population. (86) The same census reported that 71% of households primarily relied on wood or animal dung for cooking fuel. (86) The region is marked by widespread poverty, with the annual per capita income ranging between 35,000 NRs ($250) to 55,132 NRs ($394) in 2022. (87)

Study design

Trial 1 was a cluster-randomized, modified stepped-wedge trial designed to evaluate the impact of an improved biomass cookstove on reducing respiratory morbidity among children and adverse birth outcomes among pregnant women. Participants were residents of four Village Development Committees (VDCs) in the study area. The trial area was divided into 51 sectors, each containing 20–30 households and estimated to include 25–40 children younger than 36 months. These sectors were further grouped into

12 clusters, which served as the unit of randomization for the intervention. Geographic dispersion of sectors within a group was carefully considered to minimize additional clustering and outcome correlation. One cluster received the intervention per month over a 12-month period. The "modified" aspect of this trial was the addition of 6-month pre- and post-intervention outcome assessments.

Trial 2 was an individually randomized trial at the household level, designed to compare the health effects of Envirofit and LPG cookstoves. Households in two of the four VDCs were included. Each household was randomized at baseline, received the allocated intervention, and was followed for 12 months for outcome assessment. More details on study design are available elsewhere. (85)

Eligibility

In Trial 1, participants were eligible if they (1) did not already have clean cooking technologies, such as an improved, ventilated biomass, LPG, or electric cookstove; (2) used a an open-burning cookstove indoors or in an enclosed area; (3) resided in a household with mud, brick, or wood walls; (4) had either a married woman aged 15–30 years or at least one child younger than 36 months at the start of the study; and (5) provided consent and agreed to use the alternative cookstove for at least 12 months. In Trial 2, participants were eligible under the same criteria as Trial 1, except that households were required to have a child younger than 24 months at study initiation. Both participants from Trial 1 and newly eligible participants who were not included in Trial 1 were eligible to participate in Trial 2. Participants continuing from Trial 1 were given the option to transition to LPG in Trial 2, otherwise continued using the Envirofit cookstove.

Intervention

In Trial 1, participants received a commercially available two-burner biomass stove (model G-3300 with the G-3355 two-pot attachment) manufactured by Envirofit International (Colorado Springs, CO, USA), equipped with a chimney constructed from sheet metal. In Trial 2, participants were randomized to either an Envirofit biomass cookstove or an LPG two-burner stove with a gas tank and a 12-month LPG supply. Participants from Trial 1 were allowed to continue using the Envirofit stove or transition to an LPG stove. For both trials, households with thatch or bamboo walls were required to either plaster their walls with mud for proper chimney installation or accept a cookstove without a chimney.

Trial outcomes

The primary outcomes of both trials included the incidence of low birthweight among liveborn infants and acute lower respiratory illness among children < 36 months of age. Respiratory morbidity was assessed using weekly maternal or caregiver reports of child signs and symptoms. Reported symptoms included high fever, persistent cough, fast or difficult breathing, wheezing, along with non-respiratory symptoms such as watery stool, ear discharge, and burn surgery. The birthweight of infants born during the study were measured by study staff using digital infant scales (Tanita Corp., Tokyo, Japan) at the time of birth. The secondary outcomes included respiratory symptoms, blood pressure, and pulse among married women 15-30 years of age and one random adult household member older than 15 years of age, oxygen saturation, carboxyhemoglobin level, and heart rate during pregnancy, and indoor air concentrations of stove influenced and overall $PM_{2.5}$ and carbon monoxide (CO). $PM_{2.5}$ concentrations were measured over

an 18-hour period at both baseline and at the end of follow-up. Stove-influenced (SI) $PM_{2.5}$ levels were observed during cooking periods. In Trial 1, forced expiratory volumes in one second (FEV_1) and six seconds (FEV_6) of household members were also measured using the PiKo-6 pocket spirometer (nSpire Health, Longmont, CO, USA) as the additional secondary outcome.

Primary outcome definition

We assessed the incidence of respiratory morbidity among children younger than 36 months of age in Trial 1 and Trial 2. We defined each of the respiratory outcome as the following:

A child was considered to have an episode of acute lower respiratory infection (ALRI) when a child experienced a

- Fever and difficulty breathing in two or more consecutive days with both symptoms reported on at least one day during the episode and during which at least one symptom occurred each day
- Consecutive episodes must be separated by a minimum of 7 symptom free days

A child was considered to have an episode of acute respiratory infection (ARI) when a child experienced a

- Cough and difficulty breathing in two or more consecutive days with both symptoms reported on at least one day during the episode and during which at least one symptom occurred each day
- Consecutive episodes must be separated by a minimum of 7 symptom free days

A child was considered to have an episode of influenza-like illness (ILI) when a child experiences an acute respiratory infection with:

- At least one day of measured fever of ≥ 38 C° during an episode

We considered three definitions of respiratory morbidity to reflect established symptom-based case definitions used in pediatric respiratory surveillance, to enable comparability with prior studies in similar settings, and to assess the robustness of intervention effects across alternative outcome definitions in the context of caregiver-reported symptoms.

Statistical analysis

We used a modified Poisson mixed-effects model to assess the effect of the cookstove intervention on three respiratory morbidities outcomes among children aged <36 months. The intervention was included as a fixed effect. In longitudinal studies, secular trends—such as seasonality or other time-varying factors unrelated to the intervention—may confound the relationship between exposure and outcome (88, 89). To address this, we incorporated cubic splines for calendar time, with knots placed at 100-day intervals, to adjust for potential non-linear secular trends. We also accounted for the aging effect within the child cohort. Prior studies indicate that ARI risk with declines with increasing child age, likely due to immune system maturation (90, 91). We observed a similar pattern in our data and modeled age using cubic splines with knots at 6 months, 1 year, and 2 years. Random intercept for child was included to account for the clustering of observations at individual level. The primary analysis is represented as the following:

$$Y_{it} = \beta_0 + \beta(intervention)_{1i} + s(time_i) + s(age_i) + \nu(child)_{0i} + \epsilon_i$$

Let Y_{ij} denote either a log risk of respiratory morbidity for a child i = 1, …., N. In

the model, β_0 represents the overall baseline morbidity estimate, $\beta\chi_i$ represents the intervention effect on the outcome measure, $s(time_i)$ is a set of cubic splines at time t, $s(age_i)$ is a set of cubic splines of age, $v(child)_{0i}$ is a random intercept for child i to account for within-child correlation, and ϵ_i is an error term. Effect modification of sex, socioeconomic status, season of cookstove installment, smoker presence in household, and low birthweight were tested using Wald test. Household-level socioeconomic status (SES) variable was derived from key housing and asset indicators using principal component analysis (PCA), following the Demographic and Health Surveys (DHS) Wealth Index methodology. (92)

We calculated the incidence rates of each respiratory morbidity per person-year with 95% confidence intervals by month and year during the pre- and post-intervention periods in Trial 1 and between the Envirofit and LPG groups in Trial 2. Additionally, cookstove compliance rates were calculated by dividing the number of weeks in which the households reported to use the cookstove by the total number of weeks the compliance was measured. The total PM concentrations and stove-influenced PM concentrations—which were quality controlled based on humidity and gravimetric conversion— were compared between the pre- and post-intervention periods using the Wilcoxon-rank sum test.

2.3 Results

In Trial 1, a total of 4,748 children were randomized to Envirofit, of whom 3,788 and 3,525 were included in the pre-intervention and post-intervention periods, respectively. In Trial 2, 1,404 children were randomized to the Envirofit group and 1,464 to the LPG group in Trial 2. (**Figure 1**) At enrollment, 66.74% (N = 3,169) of children in

Trial 1 were under 12 months old. In Trial 2, the proportion of children under 12 months was similar between the Envirofit and LPG groups (54.13% and 54.99%, respectively). In both trials, nearly 50% of households reported farming as the primary occupation of the head of household, and 70% of mothers reported having no formal education. Trial 1 included a slightly higher proportion of poor households (31.23%) compared to the Envirofit (25.07%) and LPG (26.43%) groups in Trial 2. Sex distribution of children was nearly equal across all groups. Nearly 50% or more of households in both trials had at least 1 smoker (Trial 1 Envirofit: 60.93% vs. Trial 2 Envirofit: 50.14%, Trial 2 LPG: 48.91%). **(Table 1)**

In Trial 1, mean total PM concentrations decreased from 1,416.65 μg/m³ (SD: 1,175.68 μg/m³) before the intervention to 979.64 μg/m³ (SD: 1,138.88 μg/m³) after Envirofit stove installation, and mean stove-influenced PM concentrations declined from 3,384.44 μg/m³ (SD: 2,836.46 μg/m³) to 2,320.44 μg/m³ (SD: 2,619.75 μg/m³). Similar reductions were observed when analyses were stratified by stove location. (**Appendix A. Supplementary Table 1**) In Trial 2, mean total PM concentrations were substantially lower in households using LPG stoves compared with Envirofit stoves (460.48 μg/m³ [SD: 529.27 μg/m³] vs. 905.33μg/m³ [SD: 950.33 μg/m³]). Similarly, stove-influenced PM concentrations were lower in the LPG group (1,117.26 μg/m³ [SD: 1,273.22 μg/m³] vs. 1,347 μg/m³ [SD: 1,998 μg/m³]), with similar patterns observed across stove locations. (**Appendix A. Supplementary Table 1**) Over time, both trials demonstrated gradual reductions in PM concentrations. (**Appendix A. Supplementary Figures 1-8**) Median compliance in Trial 1 was 43.1% (IQR: 37.4%). In Trial 2, compliance was significantly higher in the LPG group compared to the Envirofit group (94.2%

[IQR: 7.9%] vs. 61.4% [IQR: 49.8%], p < 0.001). (**Appendix A. Supplementary Table 2**) Across all outcomes, seasonal incidence rates steadily decreased from 2010 to 2012, with reductions evident in every season. (**Figure 2**)

In Trial 1, the cookstove intervention was associated with modest, non-significant reductions in respiratory infection risk. ALRI decreased from 0.35 cases per person-year (PY) (95% CI: 0.32–0.37) to 0.09 cases per PY (95% CI: 0.08–0.11), an 11.6% relative risk reduction (aRR: 0.884 [95% CI: 0.665–1.173], p = 0.39). ARI incidence declined from 0.33 (95% CI: 0.31–0.35) to 0.1 (95% CI: 0.09–0.11) cases per PY, an 8.6% relative risk reduction (aRR : 0.914 [95% CI: 0.692–1.208], p = 0.53). And ILI declined from 0.26 (95% CI: 0.24–0.28) to 0.08 (95% CI: 0.07–0.09) cases per PY, an10.5% relative risk reduction (aRR: 0.895 [95% CI: 0.656–1.218], p = 0.48). (**Table 2**) The intraclass correlation coefficients (ICCs) for ALRI, ARI, and ILI were 0.269, 0.309, and 0.310, respectively, indicating modest within-participant correlation across repeated measurement. **(Table 2)**

In Trial 2, incidence rates of ALRI, ARI, and ILI were similar between the Envirofit and LPG groups. For ALRI, the rates were 0.03 cases per PY (95% CI: 0.02–0.04) in the Envirofit group and 0.02 (95% CI: 0.01–0.03) in the LPG group (aRR: 0.742 [95% CI: 0.438, 1.258], p = 0.27). ARI incidence was 0.03 (95% CI: 0.02–0.03) in Envirofit and 0.02 (95% CI: 0.02–0.03) in LPG (aRR: 0.833 [95% CI: 0.492, 1.409], p = 0.5), while ILI incidence was 0.02 cases per PY (95% CI: 0.01–0.03) in the Envirofit group and 0.02 cases per PY (95% CI: 0.01–0.03) in the LPG group aRR: 0.954 [95% CI: 0.546, 1.666], p = 0.87). (**Table 2**) Seasonal trends fluctuated between groups: the LPG group showed lower incidence in summer and monsoon, higher in autumn, and

eventually converged with Envirofit by the following summer. (**Figure 2**) Overall, one year after installation in 2013, both groups experienced nearly identical incidence rates for all three outcomes in Trial 2. The intraclass correlation coefficients (ICCs) were 0.614 for ALRI, 0.593 for ARI, and 0.559 for ILI, reflecting higher within-participant correlation across repeated measurements compared to those observed in Trial 1. **(Table 2)**

We assessed sex, socioeconomic status (SES), season of cookstove installation, smoker presence in the household, low birthweight, cookstove location as potential effect modifiers in both trials. The season of installation was identified as an effect modifier in Trial 1. The households with winter installation experienced the lowest risk of ILI following stove installation (aRR: 0.525 [95% CI 0.083, 0.974], p = 0.04), compared to those with summer (aRR: 1.875 [95% CI 0.854, 4.116], p = 0.12), monsoon (aRR: 1.083 [95% CI 0.499, 2.354], p = 0.84), and autumn (aRR: 1.696 [95% CI: 0.136, 21.175], p = 0.68) installations (p value for interaction 0.05). (**Table 3**) There was a similar intervention benefit apparent only in winter for ARIs. In Trial 2, children living in households with smokers, compared to households without smokers, experienced benefits of LPG with lower risks of ALRI (p value for interaction 0.05), ARI (p value for interaction 0.05), and ILI (p value for interaction 0.04). (**Table 4**)

2.4 Discussion

This study incorporated both a stepped-wedge trial and an individually randomized trial of alternative cookstove interventions to assess the role of cleaner cooking, and to compare different clean cooking technologies, in reducing respiratory morbidity among young children living in rural Nepal. In Trial 1, the incidence of

respiratory infections modestly declined following the cookstove intervention. In Trial 2, respiratory infection rates did not differ significantly between children using Envirofit and LPG stoves. Stove-specific and overall indoor $PM_{2.5}$ concentrations declined, with the lowest levels observed in the LPG group, though concentrations remained above WHO-recommended limits. Subgroup analyses revealed that in households with at least one smoker and those with stove installations during the winter season, were more likely to benefits from the clean cooking intervention.

Our overall findings align with previous trials. A cluster RCT in Ethiopia involving 5,508 children followed for one year found no significant reduction in acute lower respiratory infections (ALRI) diagnosed by field nurses (aOR = 0.95, 95% CI: 0.89–1.02). (76) Similarly, a trial in Malawi conducted between 2013 and 2016 reported no meaningful decrease in WHO IMCI-defined pneumonia episodes among children under five using cleaner-burning biomass cookstoves (IRR = 1.01, 95% CI: 0.91–1.13). (77) In rural Ghana, the Ghana Randomized Air Pollution and Health Study (GRAPHS) provided pregnant women with either improved biomass or LPG stoves or assigned them to a control arm. Among infants followed during their first 12 months, neither intervention significantly reduced the risk of physician-diagnosed severe pneumonia compared with controls (ICS: aRR = 1.19, 95% CI: 0.74–1.91; LPG: aRR = 0.98, 95% CI: 0.58–1.65). (93) In contrast, some studies have reported protective effects. A cluster randomized trial in Rwanda (2015–2016) evaluated portable, high-efficiency biomass-burning rocket stoves among children under five. Although the intervention did not significantly reduce 48-hour personal $PM_{2.5}$ exposure, it resulted in a 25% reduction in ARI prevalence (PR = 0.75, 95% CI: 0.60–0.93). (79) Similarly, the

Randomized Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) in highland Guatemala provided locally developed chimney stoves to households, with the primary outcome being physician-diagnosed pneumonia among children 18 months or younger. The study reported a significant reduction in severe pneumonia associated with the intervention (RR: 0.56, 95% CI: 0.31-0.97). (80)

The observed differences across studies may be attributed to several factors. The variations in stove design and differential adherence with alternative cookstove use across country, cultural, and epidemiological contexts may collectively influence the true impact of clean cooking on respiratory health. These real-world variations are difficult to control outside of tightly controlled experimental settings. For example, the Rwanda trial not only distributed improved cookstoves but also provided water filters, which likely improved overall household hygiene and reduced both diarrhea and ARI incidence yielding a compounded health benefit not seen in trials focused solely on cookstove interventions. (79) Second, intervention uptake and compliance may vary by cultural familiarity or ethnic affinity with the introduced stove relative to locally sourced designs, with stove stacking also commonly observed across trials as part of the transition towards cleaner cooking. (93, 94) Stove stacking occurs when households continue to use multiple stoves in parallel rather than relying exclusively on the intervention stove, often reflecting practical cooking needs such as preparing several dishes at the same time or accommodating different cooking functions. As a result, exclusive use of the intervention stove is likely to be lower than anticipated in real-world settings. (94, 95) Third, differences in cooking technology efficiency may contribute to variability in intervention effects. In our study, LPG stoves achieved greater reductions in $PM_{2.5}$ concentrations than

Envirofit stoves, consistent with prior evidence comparing clean fuels with improved biomass technologies. (93, 96, 97) The variation in technological performance of cookstoves likely contributes to the heterogeneous exposure reductions and health effects reported across cookstove studies. Lastly, outcome measurement approaches contribute to the variability. Some trials relied on clinical diagnoses by healthcare professionals, while others used self-reported symptoms, introducing potential inconsistencies in case definitions. Moreover, the focus on outcome severity differs across studies—some, like the Malawi and Ghana trials (77, 93), focus on severe respiratory infections while others captured more mild or broader types of respiratory infections, making direct comparisons more challenging. In this study, intervention compliance was monitored on a weekly basis, allowing for detailed characterization of stove use patterns over time. Moreover, evaluating morbidity using more than one outcome definition allowed us to examine respiratory illness patterns more comprehensively than studies relying on a single respiratory outcome, capturing a broader picture of the potential effects of cookstove interventions on respiratory health.

In our Trial 1, the greatest reductions in respiratory risk occurred with winter installations This likely reflects the combined effect of longer time spent indoors and heightened energy use during colder months, both of which increase indoor PM exposure and therefore strengthen the intervention's impact. Studies in South Asia have found that winter fuel requirements increase relative to non-winter seasons. (98-100) For instance, Lam et al. (2017) conducted seasonal fuel assessments in households located in the High Hills region of the Far-Western Development Region of Nepal, examining fuel consumption and stove types used for both cooking and non-cooking purposes. While all

households reported using wood and more than 97% identified wood as their primary fuel source each season, the average per-capita fuel consumption in winter was twice that of other measured seasons. This seasonal increase was attributed primarily to greater use of supplemental stoves, rather than the main cooking stove, to meet a range of non-meal household needs—most notably water heating and preparation of animal food. (100) These findings indicate that even if a traditional cookstove is replaced by cleaner technology, ongoing or increased use of supplemental stoves may continue to contribute substantially to household PM exposure levels, especially during winter season.

Environmental tobacco smoke is a key contributor to household air pollution (HAP) (101), and tobacco consumption remains a major public health challenge in Nepal. (102, 103) In both trials, significant proportion of the participating households had at least one smoker, resulting in higher HAP exposure among children. Such exposure has been linked in previous studies which have shown a higher risk of respiratory infections in children exposed to household tobacco smoke compared to those unexposed. (104, 105) Notably, thirdhand smoke, defined as residual tobacco smoke constituents that persist on clothing, walls, furniture, and other surfaces, can be re-emitted into the gas phase or react with other indoor pollutants to generate secondary contaminants. (104) Therefore, children living in smoking households could be inherently exposed to elevated levels of indoor pollution, regardless of where smoking occurs.

Several limitations of this study should be acknowledged. First, despite the intervention, $PM_{2.5}$ exposure levels remained well above the WHO-recommended thresholds for both stove types—10 $\mu g/m^3$ annually and 25 $\mu g/m^3$ for 24-hour exposure (106)—which may have limited the observed effects of clean cooking on respiratory

morbidity. Additional exposure sources, such as ambient air pollution and emissions from neighboring households, could also have contributed to the observed outcomes. Moreover, the low compliance rates observed in the Envirofit group in both Trial 1 and Trial 2 may have further limited the intervention's effectiveness. This pattern may reflect fuel stacking, whereby households use multiple fuels and cooking technologies according to the specific demands of a task, such as favoring LPG for cooking large meals, while relying on the mud stove when high heat or long cooking times are needed. (107) Fuel choices may also be shaped by the preferences of older heads of household, who often favor cultural and traditional cooking practices, particularly the use of firewood. (108)

It is important to note that this trial was conducted in a resource-limited context with minimal access to healthcare services. Respiratory outcomes were measured using a comprehensive set of common infection symptoms, providing a broad assessment of respiratory morbidity in settings where advanced diagnostics are not routinely available. By incorporating both subgroup analyses and comparative estimates by stove type, this study also provides large-scale empirical evidence that addresses gaps in prior research, particularly regarding how exposure reductions translate to health benefits in different household contexts. Notably, this was the first stepped-wedge trial to evaluate clean cookstoves, followed only later by *Justa* cookstove trial in Honduras (109). The stepped-wedge design provided several advantages over traditional cluster randomized trials. First, each cluster served as its own control, which improved statistical efficiency and better helped account for between-cluster heterogeneity compared to CRTs with parallel randomization. Second, the staggered rollout allowed us to account for secular trends and seasonal variations in respiratory infections, providing a more accurate estimate of

intervention effects over time. Third, the design accommodated staged implementation, which was ethically favorable, as all households eventually received the intervention despite the resource-constrained environment. (110) Lastly, respiratory morbidity data were collected weekly by trained field staff, reducing reliance on long recall periods and thereby limiting potential recall bias. Regular follow-up enabled more consistent documentation of respiratory symptoms over time and reduced variability associated with infrequent or retrospective outcome assessment.

Although the observed health benefits were modest, our findings remain important as they demonstrate an overall reduction in respiratory morbidity associated with the use of alternative cookstoves. These results highlight the public health potential of clean cooking interventions and their broader implications for improving pediatric respiratory health. Our findings may also contribute to community education efforts aimed at increasing awareness and adoption of alternative cookstoves. Raising awareness about the adverse health consequences of traditional biomass cooking is critical to facilitate behavioral change and promote the transition toward cleaner energy sources. Furthermore, these findings emphasize the need for continued government subsidies and policy support to enhance affordability and enable large-scale implementation of clean cooking interventions. Future trials should explore the long-term health impacts of clean cooking across diverse environmental and cultural settings. Also, outcomes can be more refined including laboratory-confirmed or severity-graded respiratory infection and incorporating more biomarker data to better elucidate the biological mechanisms linking air pollution reduction to respiratory health. Finally, successful policy translation will likely require a multifaceted approach that combines the provision of high-efficiency

stoves with strategies to ensure sustained adoption and engage communities to foster behavior change and long-term reduction of household air pollution exposure.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagrams of Trial 1,2

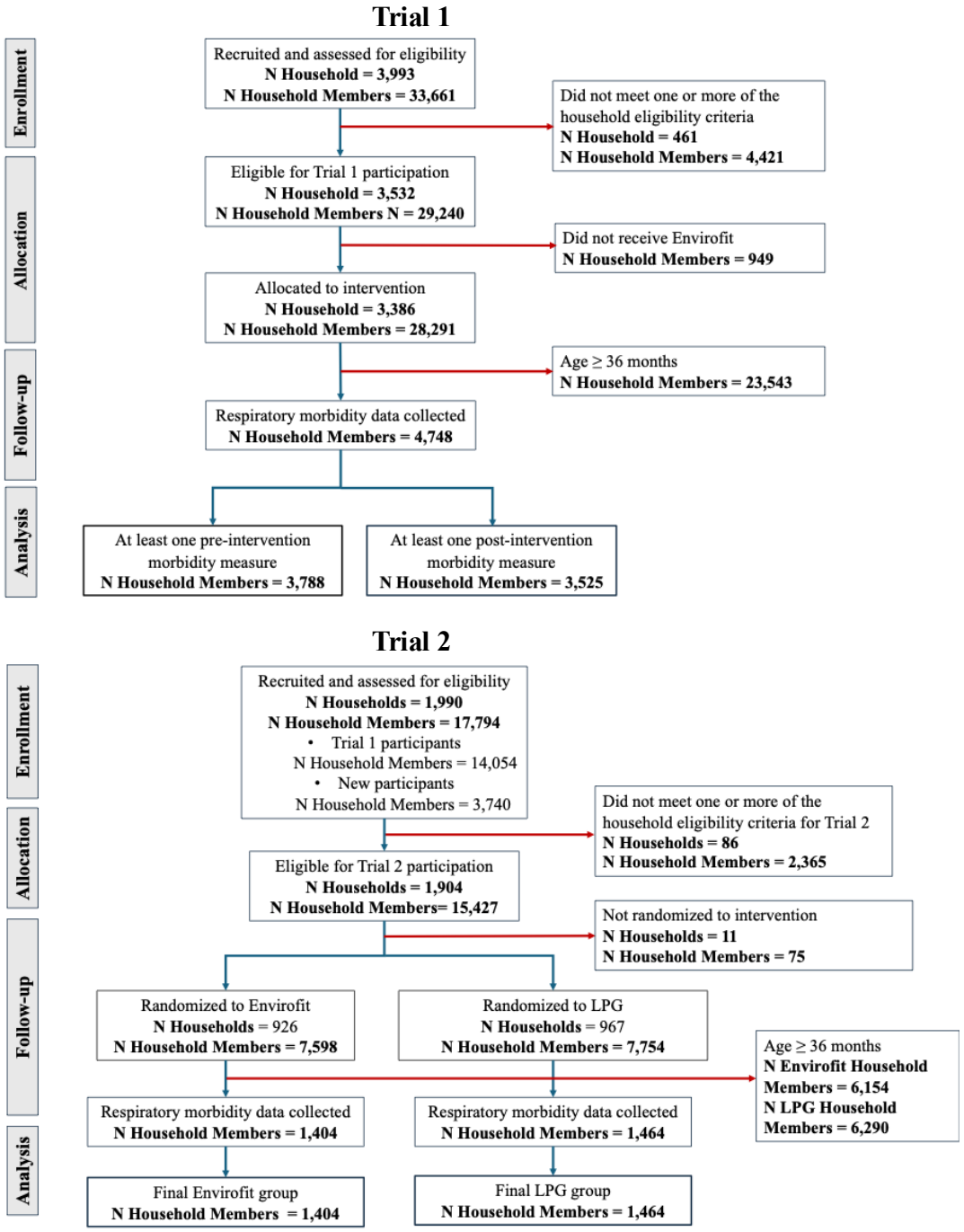
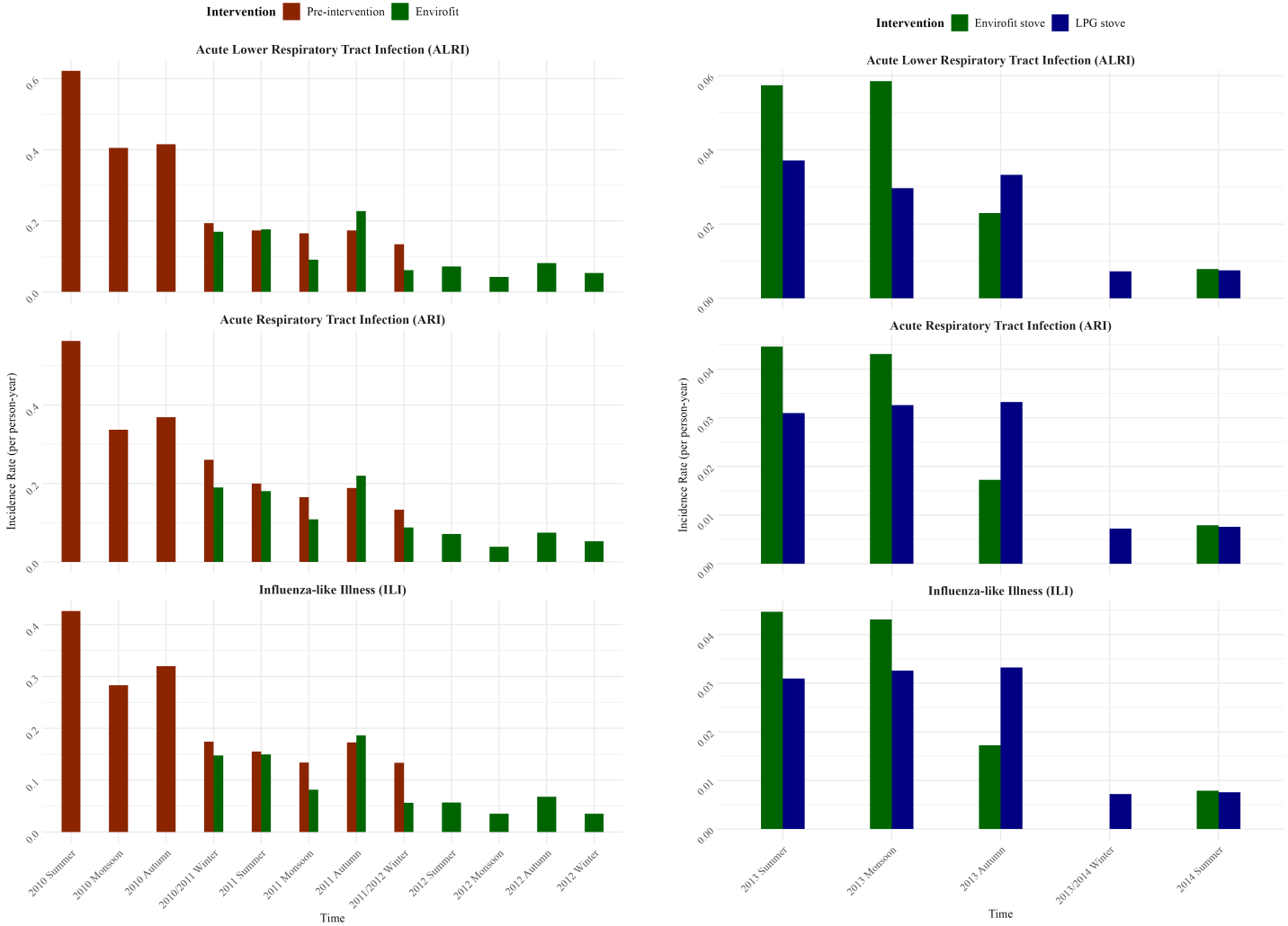


Figure 2. Seasonal incidence rates of respiratory morbidity outcomes in Trial 1,2[1,2]



1. Summer: March to May, Monsoon: June to September, Autumn: October to November
2. No data collected from the Envirofit group during 2013/2014 Winter

Table 1. Baseline characteristics of participants in Trial 1,2[1]

	Trial 1 Envirofit N (%)	Trial 2 Envirofit N (%)	Trial 2 LPG N (%)
Total number of households	2,686	948	907
Total number of children	4,748	1,404	1,464
Age groups			
< 12 months	3,169 (66.7%)	760 (54.1%)	805 (55.0%)
≥ 12 months	1,579 (33.3%)	644 (45.9%)	659 (45.0%)
Sex			
Male	2,388 (50.3%)	721 (51.4%)	749 (51.2%)
Female	2,354 (49.6%)	683 (48.7%)	715 (48.8%)
Unknown	6 (0.1%)	0 (0.0%)	0 (0.0%)
Village			
Kabilasi	1,540 (32.4%)	463 (33.0%)	468 (32.0%)
Laxmipur	1,450 (30.5%)	398 (28.4%)	414 (28.3%)
Pidari	804 (16.9%)	253 (18.0%)	264 (18.0%)
Pipariya	954 (20.1%)	290 (20.7%)	318 (21.7%)
Socioeconomic status			
Rich	1,829 (38.5%)	583 (41.5%)	578 (39.5%)
Middle	1,433 (30.2%)	469 (33.4%)	499 (34.1%)
Poor	1,483 (31.2%)	352 (25.1%)	387 (26.4%)
Unknown	3 (0.1%)	0 (0.0%)	0 (0.0%)
Maternal education			
No education	3,327 (70.1%)	984 (70.1%)	1,038 (70.9%)
1-4 years	379 (8.0%)	96 (6.8%)	69 (4.7%)
5-9 years	648 (13.7%)	196 (14.0%)	207 (14.1%)
10 years or more	388 (8.2%)	127 (9.1%)	148 (10.1%)
Unknown	3 (0.1%)	1 (0.1%)	2 (0.1%)
Head of household occupation			
Business	400 (8.4%)	168 (12.0%)	136 (9.3%)
Child/Student	132 (2.8%)	10 (0.7%)	8 (0.6%)
Contracted laborer	285 (6.0%)	178 (12.7%)	190 (13.0%)
Farmer	2,212 (46.6%)	611 (43.5%)	658 (45.0%)
Government service	53 (1.1%)	15 (1.1%)	8 (0.6%)
Housewife	50 (1.1%)	4 (0.3%)	3 (0.2%)
Private service	184 (3.9%)	33 (2.4%)	22 (1.5%)
Unskilled laborer	1,430 (30.1%)	385 (27.4%)	439 (30.0%)
Smoker in household			
Yes	2,893 (60.9%)	704 (50.1%)	716 (48.9%)
No	1,855 (39.1%)	700 (49.9%)	748 (51.1%)
Stove location			
Indoor	4,690 (98.8%)	1,174 (83.6%)	1,377 (94.1%)
Outdoor	58 (1.2%)	230 (16.38%)	87 (5.94%)
Unknown	1 (0.0%)	0 (0.0%)	0 (0.0%)
Chimney			
Yes	4,690 (98.8%)	1,404 (100.0%)	0 (0.0%)
No	58 (1.2%)	0 (0.0%)	0 (0.0%)

1. N: number of children; percentages are calculated using the total number of children as the denominator

Table 2. Effect of cookstove intervention on respiratory morbidity in Trial 1,2[1-3]

Trial	Incidence (95% CI) Cases per PY		aRR (95% CI)	p-value	ICC[4]
Trial 1	**Pre-Intervention**	**Post-Intervention**			
ALRI	0.35 (0.32, 0.37)	0.09 (0.08, 0.1)	0.884 (0.665, 1.173)	0.39	0.269
ARI	0.33 (0.31, 0.35)	0.1 (0.09, 0.11)	0.914 (0.692, 1.208)	0.53	0.309
ILI	0.26 (0.24, 0.28)	0.08 (0.07, 0.09)	0.895 (0.656, 1.218)	0.48	0.31
Trial 2	**Envirofit**	**LPG**			
ALRI	0.03 (0.02, 0.04)	0.02 (0.01, 0.03)	0.742 (0.438, 1.258)	0.27	0.614
ARI	0.03 (0.02, 0.04)	0.02 (0.02, 0.03)	0.833 (0.492, 1.409)	0.5	0.593
ILI	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.954 (0.546, 1.666)	0.87	0.559

1. Reference set as "Pre-intervention" period
2. ALRI: Acute Respiratory Lower Tract Infection, ARI: Acute Respiratory Tract Infection, ILI: Influenza-like Illness, RR: relative risk, ICC: Intraclass correlation coefficient
3. RR adjusted for cubic splines at every 100 days and random intercept for individual participant
4. ICC: Individual ICC, calculated as $\sigma^2_{individual}/(\sigma^2_{individual} + \sigma^2_{residual})$ where $\sigma^2_{residual} = \frac{\pi^2}{3}$

Table 3. Effect of Envirofit on respiratory outcomes in Trial 1, stratified by potential effect modifiers [1,2]

Variable	Acute lower respiratory tract infection (ALRI)			Acute respiratory tract infection (ARI)			Influenza-like illness (ILI)		
	aRR (95% CI)[3]	p-val	p-val[4] Int	aRR (95% CI)[3]	p-val	p-val[4] Int	aRR (95% CI)[3]	p-val	p-val[4] Int
Sex									
Male	0.74 (0.50 1.09)	0.13	0.29	0.86 (0.58, 1.26)	0.44	0.32	0.82 (0.54, 1.25)	0.35	0.42
Female	1.07 (0.71, 1.61)	0.76		0.98 (0.66, 1.46)	0.92		0.99 (0.63, 1.56)	0.97	
SES									
Poor	1.09 (0.72, 1.66)	0.7	0.27	0.92 (0.61, 1.4)	0.71	0.75	1.09 (0.7, 1.69)	0.7	0.75
Middle	0.67 (0.36, 1.27)	0.22		1.08 (0.59, 1.98)	0.8		0.82 (0.42, 1.61)	0.56	
Rich	0.87 (0.55, 1.37)	0.55		0.81 (0.52, 1.28)	0.37		0.78 (0.47, 1.3)	0.35	
Smoker									
Yes	0.87 (0.6, 1.26)	0.47	0.89	0.9 (0.63, 1.28)	0.55	0.34	0.89 (0.6, 1.33)	0.58	0.56
No	0.91 (0.58, 1.4)	0.67		0.95 (0.6, 1.5)	0.83		0.9 (0.56, 1.47)	0.68	
Birth Weight			0.44			0.14			0.66
<2500g	0.99 (0.55, 1.8)	0.98		0.92 (0.44, 1.91)	0.83		0.78 (0.38, 1.59)	0.49	
≥2500g	0.68 (0.45, 1.03)	0.07		0.66 (0.45, 0.98)	0.04		0.7 (0.44, 1.13)	0.14	
Install season[5]									
Summer	2.01 (1.01, 3.95)	0.04	0.25	1.58 (0.78, 3.18)	0.20	**0.06**	1.88 (0.85, 4.12)	0.12	**0.05**
Monsoon	1.02 (0.51, 2.04)	0.96		1.31 (0.59, 2.94)	0.51		1.08 (0.5, 2.35)	0.84	
Autumn	2.25 (0.22, 22.78)	0.49		1.94 (0.21, 17.83)	0.56		1.7 (0.14, 21.18)	0.68	
Winter	0.68 (0.4, 1.16)	0.16		0.58 (0.34, 0.99)	0.05		0.53 (0.83, 0.97)	0.04	
Stove location									
Indoor	0.88 (0.66, 1.19)	0.41	0.58	0.93 (0.7, 1.24)	0.62	0.89	0.92 (0.67, 1.27)	0.62	0.83
Outdoor	0.99 (0.37, 2.69)	0.99		0.61 (0.21, 1.82)	0.38		0.51 (0.15, 1.76)	0.29	

1. Pre-intervention group set as reference group for Trial 1
2. PY: Person-year, RR: Relative Risk, SES: Socioeconomic status
3. RR adjusted for cubic splines at every 100 days and random intercept of individual participant ID
4. p-value for interaction calculated using Wald test
5. Summer: March to May, Monsoon: June to September, Autumn: October to November

Table 4. Effect modification of respiratory outcomes in Trial 2, stratified by potential effect modifiers[1,2]

Variable	Acute lower respiratory tract infection (ALRI)			Acute respiratory tract infection (ARI)			Influenza-like illness (ILI)		
	aRR (95% CI)[3]	p-val	p-val[4] Int	aRR (95% CI)[3]	p-val	p-val[4] Int	aRR (95% CI)[3]	p-val	p-val[4] Int
Sex									
Male	0.72 (0.39,1.5)	0.39	0.94	0.76 (0.37, 1.58)	0.46	0.74	1.07 (0.49, 2.35)	0.87	0.66
Female	0.74 (0.35, 1.58)	0.44		0.91 (0.44, 1.91)	0.81		0.83 (0.38, 1.83)	0.65	
SES									
Poor	0.62 (0.29, 0.32)	0.21	0.43	0.82 (0.36, 1.87)	0.64	0.98	0.75 (0.32, 1.77)	0.51	0.64
Middle	1.18 (0.46, 3.01)	0.73		0.89 (0.39, 2.05)	0.79		1.37 (0.52, 3.59)	0.53	
Rich	0.49 (0.14, 1.74)	0.27		0.75 (0.24, 2.35)	0.63		0.88 (0.27, 2.85)	0.83	
Smoker									
Yes	0.4 (0.17, 0.94)	0.04	**0.05**	0.4 (0.17, 0.98)	0.04	**0.05**	0.46 (0.18, 1.14)	0.09	**0.04**
No	1.2 (0.58, 2.46)	0.62		1.3 (0.65, 2.6)	0.47		1.6 (0.75, 3.38)	0.22	
Stove location									
Indoor	0.83 (0.46, 1.51)	0.54	0.94	0.89 (0.49, 1.6)	0.69	0.94	1.03 (0.55, 1.93)	0.94	0.93
Outdoor	0.85 (0.24, 2.98)	0.8		0.98 (0.26, 3.61)	0.97		1.2 (0.33, 4.38)	0.78	

1. Models for birth weight did not converge due to the limited available data. For season, only summer installations were conducted
2. RR: Relative Risk, SES: Socioeconomic status
3. RR adjusted for cubic splines at every 100 days and random intercept of individual participant ID
4. p-value for interaction calculated using Wald test
5. Summer: March to May, Monsoon: June to September, Autumn: October to November

Chapter 3. Investigating the role of clean cooking on pulmonary function among individuals aged ≥10 years: Findings from a Randomized Community-Based Trial in Rural Nepal

Abstract

Background

Open-fire cookstoves remain common in rural low- and middle-income countries, generating hazardous air pollutants that impair lung function. We assessed the impact of improved cookstoves on pulmonary outcomes in Nepal.

Methods

As part of the Nepal Cookstove Intervention Project (2010–2012), a cluster-randomized, stepped-wedge trial was conducted to evaluate improved, ventilated biomass stoves (Envirofit) compared with traditional open-fire cooking. Forced expiratory volume in one second (FEV_1) and six seconds (FEV_6) were measured at baseline and end of follow-up using a PiKo-6 pocket spirometer, with three readings obtained per participant. Outcomes included pulmonary obstruction ($FEV_1/FEV_6 < 0.73$) and FEV_1/FEV_6 ratios. We used mixed-effects Poisson regression to estimate the intervention effect. Effect modification was examined by socioeconomic status, obesity, smoking, stove placement, chimney, and season of installment.

Results

A total of 5,644 participants were randomized to the cookstove intervention, comprising a population aged 10 years and older. The mean FEV_1/FEV_6 ratio increased slightly from 0.859 (SD: 0.086) before intervention to 0.861 (SD: 0.084) after stove installation.

Envirofit stoves reduced pulmonary obstruction risk by 12% (aRR: 0.88 [95% CI: 0.77–0.99], p=0.03). Autumn (aRR: 0.67 [95% CI: 0.46–0.96]) and winter (aRR: 0.68 [95% CI: 0.55–0.84) installations yielded the greater benefit compared to summer (aRR: 1.04 [95% CI: 0.84, 1.28]) and monsoon (aRR: 1.14 [95% CI: 0.89–1.4) installations (p for interaction = 0.01). Outdoor installations compared to indoor installations (aRR: 0.56 [95% CI: 0.36–0.89] vs. aRR: 0.9 [95% CI: 0.8–1.02], p for interaction = 0.02), and chimney-equipped households compared to those without chimneys (aRR: 0.87 [95% CI: 0.77–0.98] vs. aRR: 1.05 [95% CI: 0.35-3.11], p for interaction = 0.1) also showed significant reductions. Both total and stove-influenced $PM_{2.5}$ concentrations decreased following intervention, consistent across stove placement. Adherence was limited (median, 43.53%), while continued use of traditional stoves was high (median, 95%).

Conclusion

Envirofit cookstoves were associated with modest improvements in lung function on average and a 12% reduction in pulmonary obstruction, with the strongest effects observed when stoves were installed in autumn, outdoors, or with chimneys. These findings underscore the importance of context and configuration in maximizing the health benefits of cleaner cooking technologies.

3.1 Introduction

Air pollution is one of the leading causes of morbidity and mortality worldwide. Particulate matter smaller than 2.5 micrometers ($PM_{2.5}$) poses the greatest health risk by penetrating the lungs and crossing into the bloodstream. (111) Once inhaled, $PM_{2.5}$ triggers systemic inflammation by elevating plasma levels of pro-inflammatory cytokines and generating oxidative stress, processes that contribute to both acute and chronic conditions. (53, 54) Indoor air pollution from biomass fuels accounts for an estimated 4.3 million deaths annually, largely driven by stroke, ischemic heart disease, and chronic obstructive pulmonary disease (COPD). (112) Elevated PM exposures have also been linked to higher rates of pulmonary conditions such as asthma, wheezing, and other respiratory diseases. (113-115) Children and adolescents are especially vulnerable to these environmental hazards with their maturing respiratory, metabolic, and immune systems. (7, 116) Lung function continues to increase throughout these developmental stages and does not reach maximal capacity until early adulthood. (7) Consequently, exposure during these developmental intervals can alter normal pulmonary growth and predispose individuals to future respiratory disease.

Given the wide-ranging health impacts of air pollution, it is also important to consider how the intensity and context of exposure differ across settings. Seasonal variation, for example, can lead to increased fuel use and more time spent indoors during colder months, thereby elevating overall exposure levels compared to warmer seasons. (100, 117-121) Socioeconomic constraints may further limit access to cleaner fuels and well-ventilated cooking areas. (122-125) Smoking inside the home additionally raises baseline particulate levels and contributes to substantial variation in exposure and

respiratory risk across populations. (126, 127). Additionally, body mass index (BMI) has been associated with lung function and susceptibility to air pollution through alterations in respiratory mechanics and inflammatory pathways, although evidence remains limited and inconsistent. This heterogeneity in exposure and effect warrants further investigation to identify populations and contexts most likely to benefit from improved cookstove interventions.

Recognizing the magnitude of air pollution and related impacts on human health, in 2015 the World Health Organization (WHO) incorporated health indicators on household and ambient air pollution into the Sustainable Development Goals (SDGs), specifically under SDG 3 and SDG 7. (128) These targets aim to reduce deaths and illnesses attributable to air pollution and ensure universal access to clean energy. However, recent SDG progress reports indicate that achievements in these areas have been slow. (129) A significant proportion of households, particularly in South Asia and Africa, still lack access to clean energy and remain disproportionately exposed to HAP. (130)

Given the persistent burden of HAP in low- and middle-income settings, understanding its long-term respiratory health consequences remains a critical public health priority. Spirometry is the standard method for evaluating pulmonary function, providing key measures such as forced expiratory volume (FEV) and forced vital capacity (FVC). FEV reflects the volume of air exhaled during a forced breath within a specified time frame, whereas FVC captures the total volume of air expelled during a complete forced exhalation. (131) Evidence from randomized trials evaluating clean cooking technologies have shown mixed results with respect to lung function. In Mexico,

an improved wood-burning Patsari stove reduced the annual decline in FEV_1 compared with continued open-fire use, although no meaningful differences were observed in the FEV_1/FVC ratio. (132) Similarly, the RESPIRE trial in Guatemala found reductions in respiratory symptoms among women randomized to chimney woodstoves but no significant improvements in spirometric measures. (133) In contrast, a randomized trial in Rwanda found that although FVC declined across participants due to aging, the decline was significantly smaller among those receiving improved cookstoves compared with the control group (134) Overall, evidence from the previous trials suggest potential respiratory benefits of cleaner cooking technologies, but they also highlight variability across settings and the need for additional evidence.

Although lung function is traditionally evaluated using FEV_1, FVC, or their ratio (FEV_1/FVC), the FEV_1/FEV_6 ratio < 0.73 is emerging as a valid alternative to the conventional FEV_1/FVC < 0.70 threshold for diagnosing pulmonary obstruction. (135) Measuring FVC can be challenging in resource-limited settings as it requires prolonged exhalation, specialized spirometers, and trained personnel. (136, 137) By contrast, most exhalation is completed within approximately six seconds and can be measured by a portable electronic peak flow meter (138), making FEV_6 as a reliable surrogate for FVC. (139) Studies have demonstrated strong agreement between FEV_1/FVC and FEV_1/FEV_6, including Bhatt et al. (2013), who reported excellent concordance in diagnosing between COPD-related morbidity and CT-assessed structural lung disease ($\kappa = 0.9$ [95% CI: 0.80–0.91], $p < 0.001$) (140), and Melbye et al. (2006), who showed that FEV_1/FEV_6 cutoff of 73% corresponded closely to an FEV_1/FVC of 70%. (141) A meta-analysis by Jing et al. (2009) further confirmed the diagnostic utility of FEV_1/FEV_6 for airway obstruction,

reporting high sensitivity (0.89) and specificity (0.98) of the ratio. (137)

The FEV_1/FEV_6 ratio is a practical diagnostic marker of pulmonary obstruction and was used in this study as the primary indicator of lung function. Given that household air pollution from biomass fuel remains a major contributor to impaired respiratory health in low-resource settings, this randomized trial evaluated the impact of a clean cookstove intervention on lung function as a secondary outcome among residents in rural Nepal. Additionally, we examined whether the intervention's effects varied across population subgroups, offering insight into differential benefits of clean cooking technologies.

3.2 Methods

Study Population

The Nepal Cookstove Intervention Project (NCT00786877) consisted of two randomized trials designed to evaluate the impact of clean cooking technologies on improving air quality, childhood respiratory morbidity, and reproductive outcomes among residents of the Sarlahi District in the Terai region of southern Nepal. The Terai is a densely populated, predominantly rural floodplain of the Ganges River, where most residents rely on farming or other labor-intensive occupations. (142) Literacy remains low, particularly among women. According to the 2021 national census, approximately 40% of the district's population reported being illiterate, with women comprising 60% of this group. (143) The same census indicated that 71% of households relied on solid fuels such as wood or animal dung as cooking fuel. (143) Poverty is widespread, with annual per capita income ranging from 35,000 NRs ($250) to 55,132 NRs ($394) in 2022. (144)

Study Design

The first trial was a cluster-randomized, modified stepped-wedge trial assessing

the effects of an improved biomass cookstove on respiratory morbidity in children and adverse birth outcomes among pregnant women. The study was conducted in four Village Development Committees (VDCs) and divided into 51 sectors, each containing 20–30 households and an estimated 25–40 children under 36 months. These sectors were grouped into 12 clusters, serving as the unit of randomization. Clusters were geographically distributed to minimize additional correlation in outcomes. One group received the intervention each month over a 12-month period, with outcome assessments conducted six months before and after intervention implementation. More details on study design are available elsewhere. (142)

Eligibility

The households were eligible if they (1) did not already use clean cooking technologies (e.g., improved ventilated biomass, LPG, or electric stoves), (2) used an open-burning cookstove indoors or in an enclosed space, (3) had walls constructed from mud, brick, or wood, (4) had either a married woman aged 15–30 years or at least one child younger than 36 months at baseline, (5) provided informed consent and agreed to use the intervention stove for at least 12 months. Participants were eligible for spirometry if they were not pregnant, did not have tuberculosis (TB) or were receiving TB medication, had not experienced a respiratory infection in the past 14 days, and did not report a chronic cough with night sweats lasting longer than 14 days. If an invalid FEV measurement occurred, additional attempts were made, with a maximum of eight measurements per participant, with the goal of obtaining up to three valid measurements. Only participants who received Envirofit stove were eligible for inclusion in the analysis.

Intervention

In the trial, households received a commercially available two-burner biomass stove (model G-3300 with G-3355 two-pot attachment) manufactured by Envirofit International (Colorado Springs, CO, USA), fitted with a metal-sheet chimney. Households with thatch or bamboo walls were required to plaster walls with mud for chimney installation or otherwise accept a stove without a chimney.

Trial Outcomes

The primary outcomes included maternal reports of respiratory symptoms and other morbidities among children younger than 36 months. In addition, indoor air concentrations of stove influenced and overall $PM_{2.5}$ and carbon monoxide (CO) levels, infant birthweight and gestational age were recorded. $PM_{2.5}$ concentrations were measured over an 18-hour period capturing cooking events at both baseline and at the end of follow-up. Stove-influenced (SI) concentrations were defined as $PM_{2.5}$ levels observed during cooking periods. More detailed descriptions of the primary and secondary outcomes are reported elsewhere. (142) In the trial, forced expiratory volume in one second (FEV_1) and six seconds (FEV_6) were measured using a PiKo-6 pocket spirometer (nSpire Health, Longmont, CO, USA). Measurements were conducted at baseline and at the end of follow-up, primarily for married women 15-30 years of age and one other randomly selected household member who was 15 years or older. However, measurements were also obtained from participants younger than 15 years of age as part of an additional data collection effort. At each time point, field workers obtained three readings per participant for each parameter.

Primary outcome definition

The primary outcomes of this study are the FEV_1/FEV_6 ratio and pulmonary obstruction as defined by $FEV_1/FEV_6 < 0.73$ among participants 10 years or older. The obstruction was calculated as the ratio of the average of the first three valid FEV_1 measurements to the average of the first three valid FEV_6 measurements. If any of the first three attempts were flagged as invalid, they were replaced with the next available valid measurement, up to a total of three valid measurements. Children under 10 years were excluded from the primary outcome analysis due to concerns around the reliability and reproducibility of FEV measurements in younger age groups. Additionally, participants with an $FEV_1/FEV_6 \geq 1$ were excluded, as such values are physiologically implausible and likely indicative of measurement error or poor technique.

Variables

Demographic information including age, sex, literacy, and smoking status was collected at enrollment. The head of household was defined as the oldest male; if unavailable, the oldest female was selected. In cases where individuals were of the same age, the person with the higher occupational status was designated. Head of household literacy was similarly determined by the highest literacy level of the oldest male or female. Socioeconomic status (SES) was derived following the Demographic and Health Surveys (DHS) methodology using principal component analysis of key household and asset indicators, with the first principal component used to create SES quintiles. Season of installation was derived from the recorded stove installation date and assigned according to the corresponding calendar month, with Summer defined as March to May, Monsoon as June to September, Autumn as October to November, and Winter as

December to February. Following WHO body mass index (BMI) criteria for Asian populations, participants were classified as obese if their BMI was ≥ 27.5 kg/m² and as non-obese otherwise. (145)

The Envirofit stove was designed with a chimney, but this feature posed a fire hazard in homes with thatch walls or ceilings, which were common in the study area. If participants agreed to reinforce their walls with mud, the chimney was installed; otherwise, a chimneyless version was provided. The intervention cookstoves were placed in either indoors or outdoors.

Statistical analysis

We employed a modified Poisson mixed-effects model with robust variance estimation to estimate relative risks and 95% confidence intervals (CIs) of pulmonary obstruction. The intervention was specified as a fixed effect. Covariates included sex, cubic splines of age (modeled in 10-year increments from 10 to 90 years), and height categorized into quartiles based on the study population distribution (first quartile: 147 cm; median: 152 cm; third quartile: 158 cm). A random intercept for each household address was incorporated to account for within-household correlation from the pre- and post-intervention measurements.

Sex was included to adjust for physiological differences in lung capacity, as females generally have smaller lungs, reduced airway diameters, and lower flow rates compared to age- and height-matched males. (146, 147) Height was included to capture the proportional relationship between body size and lung function, given that taller individuals typically have larger lung volumes and higher expiratory flow rates. (148) Age was modeled flexibly with splines to reflect the non-linear decline in lung function

over time. (149) In our data, both height and age demonstrated non-linear associations with the FEV_1/ FEV_6 ratio.

$$Y_{it} = \beta_0 + \beta(intervention)_{1i} + \beta(sex)_{2i} + s(age_i) + s(height_i) + v(household)_{0i} + \epsilon_i$$

Let Y_{ij} denote either a log risk of pulmonary obstruction for a participant i = 1, …., N. In this model, β_0 represents the overall baseline pulmonary obstruction estimate, $\beta\chi_i$ represents the intervention effect on the outcome measure, $s(time_i)$ is a set of cubic splines at time t, $s(age_i)$ is a set of cubic splines of age, $v(household)_{0i}$ is a random intercept for participant i to account for within-household correlation, and ϵ_i is an error term.

Effect modification was assessed using Wald tests comparing full and reduced models for each of the following characteristics: SES, obesity, presence of at least one smoker in the household, cookstove location, presence of a chimney with the installed stove, and season of cookstove installation. In addition, pre- and post-intervention FEV_1/FEV_6 values were compared using the Wilcoxon rank-sum test, with mean differences and corresponding 95% confidence intervals reported. $PM_{2.5}$ concentrations were similarly compared before and after the intervention. Finally, adherence with the Envirofit stove use was calculated as the proportion of weeks, from date of stove installation until the end of the trial, that the assigned stove was reported in use.

3.3 Results

The study initially identified 5,644 participants randomized to the cookstove intervention. Participants were excluded if they were ineligible for the trial or lacked PiKo measurements, as the measurement was conducted in only a subset of household members and some individuals were ineligible for assessment. Among those with

available data, additional exclusions were applied for those with less than three sets of valid FEV measurements, age younger than 10 years, and FEV ratio ≥ 1. After these exclusions, 5,263 (93%) participants contributed data in the pre-intervention period and 4,337 (77%) in the post-intervention period. (**Figure 3**)

At baseline, most participants were female (70.5%), and the median height was 152cm (IQR: 10cm). Farming was the predominant occupation (48.8%), followed by unskilled labor (27.8%). In this population, more than 65% of heads of households reported to be illiterate (65.7%). Approximately one-third of participants resided in households with at least one smoker (33.9%) and at least one obese person (31.4%). (**Table 5**)

The mean FEV_1/ FEV_6 ratio showed a modest increase from 0.859 (SD 0.086) at baseline to 0.861 (SD: 0.084) following stove installation. A significant improvement was noted among participants who received stoves during the winter season, with mean values increasing from 0.858 (SD: 0.090) to 0.872 (SD: 0.077) and those with outdoor installation, with mean values increasing from 0.854 (SD: 0.095) to 0.868 (SD: 0.084). (**Appendix B, Supplementary Table 4**)

After adjusting for age, height, sex, the Envirofit cookstove was associated with a 12% reduction in pulmonary obstruction risk (aRR: 0.88 [95% CI: 0.77–0.99], p = 0.03), with an intraclass correlation coefficient (ICC) of 0.08. (**Table 6**) Subgroup analyses identified significant effect modification by season of installation (p-value for interaction = 0.01), stove location (p-value for interaction = 0.02), and chimney installation (p-value for interaction = 0.1). The largest reduction in risk of pulmonary obstruction was observed among households with autumn (aRR: 0.67 [95% CI: 0.46–0.96]) and winter

(aRR: 0.68 [95% CI: 0.55–0.84]) installations. Greater reductions were also found among households with outdoor (aRR: 0.56 [95% CI: 0.36–0.89]) as compared to indoor (aRR: 0.9 [95% CI: 0.8–1.02]) installations and those with chimney (aRR: 0.87 [95% CI: 0.77–0.98]) as compared to those without chimneys (aRR: 1.05 [95% CI: 0.35–3.11]). (**Table 6**)

Both total and stove-influenced $PM_{2.5}$ concentrations decreased following the installation of Envirofit stoves, with mean reductions of 32.3% and 35.1%, respectively. These reductions were consistent across subgroups, ranging from mean 30.4% to 35.1%. The largest reduction was observed for overall stove-influenced $PM_{2.5}$, which declined by 35.1%. At baseline, exposures were higher in households with indoor kitchens, regardless of chimney presence. There were no $PM_{2.5}$ measurements available for households without chimneys. (**Table 7**) Intervention compliance was relatively low, with a median usage of 43.53% (IQR: 37.2), while continued reliance on traditional cookstoves remained widespread, as 94.64% of households (IQR: 15.32%) reported concurrent use of non-intervention stoves during the study period.

3.4 Discussion

In this study, we assessed the role of cleaner cooking technology on lung function of individuals 10 years or older living in households with heavy reliance on traditional, open-fire cooking. In this cluster randomized trial, we observed an overall improvement in lung function, reflected by an increase in the mean FEV_1/FEV_6 ratio, together with significant reductions in the risk of pulmonary obstruction following the installation of Envirofit stoves. Subgroup analyses indicated that these improvements were most pronounced among households where stoves were installed during the winter season.

Additional benefits were also more evident among households with outdoor installations and those equipped with chimneys, underscoring the importance of both the timing and physical configuration of stove placement in maximizing health outcomes.

The observed reductions in pulmonary obstruction associated with cleaner stove technologies are consistent with findings from previous studies. A cluster-randomized controlled trial conducted in rural villages of southwest China in 2019 evaluated the pulmonary benefits of installing ventilation hoods during cooking. Lung function was assessed using an electronic spirometer and compared between baseline and follow-up visits across intervention and control groups. The study reported a significant improvement in lung function, with an 8% increase in FEV_1/FVC (8% [95% CI: 0.7%–15.2%]; $p < 0.05$). Moreover, a significant dose–response relationship was observed with reductions in $PM_{2.5}$ exposure: each interquartile range decrease in the 95th percentile of 24-hour $PM_{2.5}$ levels was associated with a 2% increase in FEV_1/FVC (95% CI: 0.1%–4%; $p < 0.05$). (150) Similarly, a cross-sectional study conducted in rural India between 2009 and 2010 compared households using biomass fuel versus LPG as their primary cooking fuel and assessed lung function among women using spirometry. The study found significantly lower FEV_1/FVC ratios among biomass users compared with those using LPG (raw spirometric data: -7% (3.4%), $p = 0.04$). Moreover, the decline in lung function with age was steeper among biomass users ($p = 0.01$), suggesting cumulative exposure effects from prolonged use of solid fuels. (151) A retrospective cohort study conducted in Xuanwei, China between 1976 and 1992 assessed whether improvements in coal stoves with chimney installation reduced the risk of COPD among farmers who were lifelong users of smoky coal. Compared with those who continuously used unvented

stoves, the study demonstrated that the presence of chimneys was associated with a significantly lower risk of self-reported COPD in both men (RR: 0.58 [95% CI: 0.49–0.70], $p < 0.001$) and women (RR: 0.75 [95% CI: 0.62–0.92], $p = 0.005$). (152)

Seasonal variation in environmental factors likely contributed the observed reduction in pulmonary obstruction risk during autumn winter compared to other seasons. The increases in PM concentrations during post-monsoon seasons have been reported in Nepal across both urban and rural areas. (153, 154) During cold and dry months, the air pollution levels can increase and persist longer in the atmosphere, which can inhibit dispersion and trap particulate matter near ground level. (118, 120, 155) In addition, reliance on solid fuels for heating and shifts in daily activity patterns during colder months further elevate exposure, compounding the health risks associated with indoor and outdoor air pollution. (100, 121) Lam et al. (2017) reported that per-capita fuel use in the High Hills region of Nepal nearly doubled in winter compared with other seasons, largely due to supplemental stoves used for heating water and preparing animal food. (100) Likewise, Islam et al. (2022) found that biomass burning contributed substantially to wintertime $PM_{2.5}$ concentrations in the Kathmandu Valley (10–17%), second only to fossil fuel combustion (14–26%). Consistent with this, a year-long study in 2006 on the outskirts of Kathmandu Valley documented markedly higher outdoor $PM_{2.5}$ levels in winter, peaking in February (~50 $\mu g/m^3$), with the lowest levels during the monsoon (~10 $\mu g/m^3$). (121) Shakya et al. (2014) similarly observed that $PM_{2.5}$ concentrations were on average 3.6 times higher during the dry winter season compared with the monsoon at an urban residential site in Lalitpur. (156) Taken together, these seasonal dynamics may help explain the largest reductions in pulmonary obstruction in our study observed among

households receiving stove installations during the autumn and winter months, making reductions in pollution particularly impactful.

In this study, we found no evidence of interaction between obesity and the intervention. Nonetheless, prior studies suggest that being underweight may increase susceptibility to air pollution and is associated with a synergistic adverse effect of air pollution on lung function, although the underlying biological mechanisms remain poorly understood. (157, 158) A cross-sectional study in India evaluating children's lung function by air pollution level in two areas reported that underweight and obese children were similarly vulnerable to air pollution. In West Bengal, a relatively low-pollution region, 30% of underweight and 33.3% of obese children had abnormal lung function. In contrast, in Delhi, where pollution levels are high, 50.1% of underweight and 55.6% of obese children exhibited impaired lung function. (159) Comparable findings were noted in a German birth cohort, where mean FEV_1 and FVC values at age 15 were lowest among underweight children (3.1 L and 3.5 L), compared with normal-weight peers (3.5 L and 4.0 L) and overweight/obese adolescents (3.7 L and 4.4 L). (160) Several explanations may account for these patterns. Underweight individuals often exhibit reduced skeletal muscle mass, particularly in the diaphragm, intercostal, and abdominal muscles, which can compromise respiratory muscle strength and limit pulmonary function. (158) Furthermore, lower circulating antioxidant levels are frequently documented among underweight populations, particularly in LMICs, where malnutrition can exacerbate oxidative stress. (161-163) This heightened oxidative burden, combined with reduced lung capacity, may amplify susceptibility to the adverse respiratory effects of air pollution.

In Nepal, most households continue to rely on solid fuels, often burned inside poorly ventilated kitchens. (164, 165) According to the 2022 DHS Nepal report, 61.7% of households reported cooking indoors, and among these, 22.7% lacked a separate room or designated kitchen. (165) Similarly, in our study, 81.7% of households had indoor kitchens. Cooking in enclosed spaces without adequate ventilation causes rapid accumulation of air pollutants, resulting in sharp spikes of HAP. Such indoor cooking conditions may help explain why the protective association was attenuated among households with indoor installations in our study. However, the small number of households with outdoor installation in this study limits the interpretation of this result. Elevated indoor PM exposure persisted even among households with chimneys, where concentrations remained higher than outdoor levels at both baseline and follow-up. However, our results also demonstrated that improved cookstoves equipped with chimneys significantly reduced HAP, consistent with findings from other randomized trials. Although PM measurements were not available for households without chimneys in our study, evidence from comparable trials indicates that improved cookstoves provide meaningful reductions compared with traditional stoves. Together, these results indicate that improvements in lung function require not only cleaner stove technologies but also attention to stove placement and ventilation. Addressing both factors is essential to lowering the burden of pulmonary obstruction in populations reliant on solid fuels.

To date, this is the first study to apply the FEV_1/FEV_6 ratio as an alternative marker of airway obstruction to evaluate the effect of improved cookstoves, despite prior evidence supporting the validity of this ratio. It is also among the few randomized trials assessing the impact of clean cooking technologies on pulmonary function. In Nepal,

COPD prevalence remains high, likely shaped by the combined burden of household and ambient air pollution and smoking. (166, 167) The uptake of clean cooking solutions has also been limited, particularly in rural areas with poor access to cleaner commercial fuels and existing cultural barriers to new technologies. (108, 168, 169) Within this context, our study addresses a critical evidence gap by demonstrating the potential of clean cooking interventions to improve pulmonary health and underscoring the need for stronger institutional support to expand clean cooking initiatives in the region.

Several limitations and strengths of this study should be acknowledged. First, some participants lacked valid FEV measurements due to loss to follow-up, limiting paired comparisons over time. Second, the FEV_1/FEV_6 ratio alone cannot establish a definitive diagnosis of COPD, as it remains a surrogate; further clinical evaluations are necessary for confirmation. Thus, our outcome reflects risk of obstruction rather than clinical COPD. Third, $PM_{2.5}$ levels during the study period remained well above WHO-recommended thresholds (10 μg/m³ annually and 25 μg/m³ for 24-hour exposure) (170), with baseline concentrations far exceeding guideline values, as also observed in our previous study that assessed the $PM_{2.5}$ at baseline. (171) This likely reflects the continued use of non-intervention stoves and contributions from neighboring household smoke, factors that may have confounded the true effects of intervention. However, this was a randomized trial conducted in one of the poorest regions of Nepal. In this setting, where skilled personnel for spirometry were not available across all areas, the use of portable device provided a pragmatic approach in assessing lung function of study participants. Finally, a broader limitation in this field is the absence of standardized reference ranges for healthy lung function, as existing predictive equations for forced expiratory volumes

vary by population characteristics including race, sex, age, and height as well as by the statistical methods used in their derivation.

Despite increasing recognition of the need for cleaner household energy, efforts to expand clean cooking remain constrained by multiple barriers. The high cost of alternative fuels and the maintenance of improved stoves can be prohibitive, and cultural preferences may hinder adoption. For example, liquefied petroleum gas (LPG) can cost the equivalent of a substantial share of a household's monthly income, making it unaffordable without sustained subsidies among those living in rural areas. (172) In addition, governments often face budget constraints in supporting clean stove initiatives, and in many rural areas, limited infrastructure such as unreliable electricity access further restricts the feasibility of new technologies. (168, 173) These constraints underscore the need for robust evidence to support global efforts to accelerate the transition away from solid fuels. However, evidence from randomized trials of improved or alternative cookstoves remains inconsistent across health outcomes and populations. For respiratory outcomes beyond spirometric measures, including pneumonia, evidence of benefit has been limited. For example, a randomized trial in Malawi found no reduction in childhood pneumonia incidence following the introduction of cleaner-burning biomass cookstoves. (77) Similarly, a randomized trial in Ghana by Jack et al. reported no improvements in birth weight and no reduction in severe pneumonia risk during the first year of life following LPG or improved cookstove interventions. (174) In contrast, a cluster randomized trial in Bangladesh observed reductions in low birth weight and lower maternal blood carboxyhemoglobin levels among pregnant women using improved cookstoves. (175) Evidence for other outcomes also remains limited, for example, with

randomized studies in Nicaragua using improved biomass stoves and in India using ethanol stoves reporting no meaningful reductions in blood pressure among women previously using the open fire cookstoves. (176)

In summary, our findings indicate that use of an improved cookstove was associated with improvements in pulmonary function. When considered alongside prior randomized trials reporting mixed effects across a range of health outcomes, our results suggest that detectable health benefits may depend on the outcome assessed, the extent of exposure reduction achieved, and contextual factors influencing sustained stove use. Together, this evidence highlights the need to further delineate the conditions under which cleaner cooking technologies translate into sustained and clinically meaningful health benefits. Future research should build on these findings by evaluating clean cooking interventions across diverse geographic settings where open-fire cooking remains prevalent, incorporating longer follow-up periods to assess durability of health effects, and, where feasible, integrating clinically validated pulmonary outcomes to strengthen the robustness and generalizability of the evidence base.

Figure 3. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

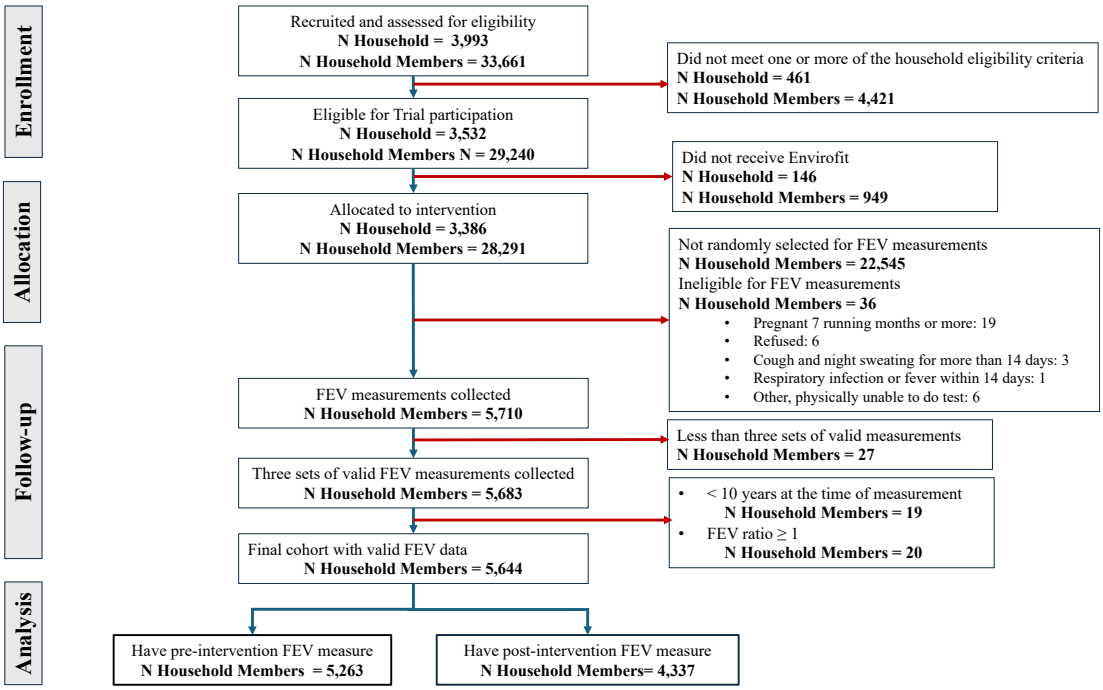


Table 5. Baseline characteristics of participants in Trial 1

Characteristics	N (%)[1]
Total number of participants	5,644 (100%)
Age groups	
< 18 years	366 (6.5%)
18-25 years	1,913 (33.9%)
26-39 years	2,266 (40.2%)
40-59 years	911 (16.1%)
≥ 60 years	188 (3.3%)
Height (cm, Median [IQR])	152 (10.0)
Sex	
Male	1,664 (29.5%)
Female	3,980 (70.5%)
Socioeconomic status	
Higher	2,116 (37.5%)
Middle	1,815 (32.2%)
Poor	1,712 (30.3%)
Unknown	1 (0.0%)
Head of household literacy	
Literate	1,935 (34.3%)
Illiterate	3,709 (65.7%)
Head of household occupation	
Business	500 (8.9%)
Child/Student	151 (2.7%)
Contracted laborer	335 (5.9%)
Farmer	2,753 (48.8%)
Government service	72 (1.3%)
Housewife	52 (0.9%)
Private service	211 (3.7%)
Unskilled laborer	1,570 (27.8%)
Smoker in household	
Yes	1,914 (33.9%)
No	3,730 (66.1%)
Obese[2]	
Yes	1,771 (31.4%)
No	3,782 (67.0%)
Unknown	91 (1.6%)

1. N = Number of participants, IQR: Interquartile range
2. Obesity was defined as having a body mass index (BMI) greater than 27.5

Table 6. Effect of cookstove intervention on pulmonary obstruction[1,2]

	Prevalence of pulmonary obstruction		aRR (95% CI)[5]	p-val	p-val[6] Int
	Pre-intervention N (%)[3,4]	Post-intervention N (%)[3,4]			
Total[7]	5,263 (100%)	4,337 (100%)	-	-	-
Overall	381 (7.24%)	312 (7.19%)	0.88 (0.77, 0.99)	0.03	-
Smoker in household					0.59
Yes	182 (3.46%)	146 (3.37%)	0.85 (0.72, 1.01)	0.06	
No	199 (3.78%)	166 (3.83%)	0.91 (0.76, 1.08)	0.28	
SES					0.89
Poor	130 (2.47%)	104 (2.4%)	0.89 (0.71, 1.11)	0.3	
Middle	134 (2.55%)	107 (2.47%)	0.86 (0.71, 1.04)	0.12	
High	117 (2.22%)	101 (2.33%)	0.89 (0.72, 1.1)	0.28	
Obese[8]					0.62
Yes	164 (3.12%)	133 (3.07%)	0.9 (0.76, 1.07)	0.23	
No	213 (4.05%)	179 (4.13%)	0.87 (0.73, 1.04)	0.12	
Season					0.01
Summer	103 (1.96%)	103 (2.37%)	1.04 (0.84, 1.28)	0.74	
Monsoon	91 (1.73%)	87 (2.01%)	1.14 (0.89, 1.45)	0.31	
Autumn	47 (0.89%)	28 (0.65%)	0.67 (0.46, 0.96)	0.03	
Winter	140 (2.66%)	94 (2.17%)	0.68 (0.55, 0.84)	< 0.001	
Cookstove location					0.02
Indoor	351 (6.67%)	294 (6.78%)	0.9 (0.8, 1.02)	0.11	
Outdoor	30 (0.57%)	17 (0.39%)	0.56 (0.36, 0.89)	0.01	
Chimney installed					0.1
Yes	374 (7.11%)	304 (7.01%)	0.87 (0.77, 0.98)	0.02	
No	7 (0.13%)	7 (0.16%)	1.05 (0.35, 3.11)	0.93	

1. RR: Relative, SES: Socioeconomic Status, Season: Summer runs from March to May, Monsoon runs from June to September, Autumn runs from October to November, and Winter runs from December to February
2. Pulmonary obstruction defined as $FEV_1/FEV_6 < 0.75$
3. N: Number of participants with pulmonary obstruction, %: Number of participants with pulmonary obstruction divided by total number of participants in each variable level by intervention status
4. Participants with missing values in each subgroup were omitted
5. Adjusted for age cubic splines with knots at every 10 years old from 10-90 years old, height cubic splines with knots at the first quartile (147cm), median (152cm) and third quartile (158cm) of study population height distribution, sex, and random intercept of individual participant ID
6. p-value for interaction calculated using Wald test
7. Total number of participants in pre-intervention, post-intervention periods
8. Obesity was defined as having a body mass index (BMI) greater than 27.5

Table 7. Total and stove-influenced median PM concentrations by intervention status[1,2]

PM type (ug/m^3)	Pre-intervention			Post-intervention		
	N	Median (IQR)	Mean (SD)	N	Median (IQR)	Mean (SD)
Overall						
Total	2,837	1126 (1204.5)	1437.27 (1278.75)	2,712	688 (845.75)	973.56 (1128.51)
Stove-influenced		2744 (3101.75)	3497.99 (3214.49)		1594 (2141)	2270.9 (2522.94)
Indoor stove						
Total	2650	1120 (1219)	1440.22 (1289.92)	2543	682 (851)	976.96 (1143.81)
Stove-influenced		2742 (3125)	3243.48 (3243.78)		1575 (2121)	2267.06 (2542.65)
Outdoor stove						
Total	183	1201 (957)	1405.26 (1105.66)	167	769 (393)	930.68 (854.91)
Stove-influenced		2784 (2978)	3463.36 (2761.09)		1831 (2246)	2356.13 (2197.5)
Chimney installed						
Total	2794	1130 (1201)	1433.34 (1244.94)	2712	688 (845.75)	973.56 (1128.51)
Stove-influenced		2747 (3109)	3481.43 (3041.08)		1594 (2141)	2270.9 (2522.94)
Chimney & indoor						
Total	2621	1122 (1223)	1437.01 (1253.08)	2543	682 (851)	976.96 (1143.81)
Stove-influenced		2747 (3132)	3489.26 (3059.2)		1575 (2121)	2267.06 (2542.65)
Chimney & outdoor						
Total	172	1182 (911.5)	1385.09 (1112.97)	167	769 (757)	930.68 (854.91)
Stove-influenced		2749 (2727)	3384. 23 (2748.65)		1831 (2246)	2356.13 (2197.5)

1. N = Number of households
2. All comparisons were statistically significant ($p < 0.01$), with p-values calculated using the Wilcoxon rank-sum test

Chapter 4. Evaluating the Population-Level Impact of Pneumococcal Conjugate Vaccine Introduction and Coverage on Acute Respiratory Infection and Antibiotic Use Among Children in Low- and Middle-Income Countries

Abstract

Background

Acute respiratory infection (ARI) remains a leading cause of morbidity and mortality among children under five years of age. Although ARI includes both viral and bacterial etiologies, antibiotics are frequently prescribed for its treatment. The pneumococcal conjugate vaccine (PCV) targets *Streptococcus pneumoniae*, a major bacterial cause of severe ARI. However, its impact on overall ARI burden and antibiotic use remains unclear. This study aimed to assess whether PCV introduction and coverage were associated with changes in ARI prevalence, antibiotic use, and under-five mortality rate among young children in low- and middle-income countries.

Methods

We analyzed data from the Demographic and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS), including children aged 6–35 months. Primary outcomes were ARI prevalence, antibiotic use during ARI, and absolute risk differences in ARI and antibiotic use between pre- and post-PCV periods. ARI was defined as maternal report of cough with fast or difficult breathing, excluding isolated nasal congestion. Antibiotic use was defined as reported receipt of antibiotics during ARI symptoms, with antibiotic use during diarrhea examined as a negative outcome. Risk differences were calculated as the absolute difference in outcome prevalence between pre- and post-PCV periods within each country-year. The secondary outcome included under-five mortality rates, which were extracted from each survey and reported as deaths

per 1,000 live births in the five years preceding the survey. The primary exposure was PCV introduction status, defined as a binary indicator of whether a country had introduced PCV at the time of survey, and country-level PCV coverage (PCV1, PCV2, and PCV3), defined as the proportion of children who received each dose based on vaccination cards or records. Quasi-Poisson and linear regression models with country-clustered standard errors were used, adjusting for urban population prevalence, time since PCV introduction, solid fuel use prevalence, diphtheria- or pentavalent-vaccine coverage, public care-seeking prevalence, and prevalence of none and primary maternal education levels combined. Subgroup analyses by age group and country income level were performed, with interaction terms assessed using Wald tests and country-clustered standard errors.

Findings

We included 97 surveys conducted between 2005 and 2023 across 40 countries with universal PCV implementation. The mean duration since PCV introduction was 3.8 ± 3.7 years. 33 countries currently use PCV13, and 34 maintain a three-primary-dose schedule. Across countries, both ARI prevalence (PR: 0.7 [95% CI: 0.69, 0.72; $p < 0.01$]) and antibiotic use (PR: 0.78 [95% CI: 0.75, 0.81; $p < 00.01$]) were lower in post-PCV periods, with consistent patterns across age groups and income categories. Although mean PCV coverages fluctuated over the study period, the overall trend showed a gradual increase until 2019. PCV introduction was associated with a 1.7 percentage point reduction in ARI prevalence ($a\beta$: −0.017 [95% CI: −0.029, −0.005], $p = 0.01$]) and 24% lower ARI prevalence (aPR: 0.76 [95% CI: 0.646, 0.901], $p = 0.002$) compared with the pre-PCV period. An increase in PCV1, PCV2, and PCV3 coverage were associated with

reduced ARI prevalence (PCV1 aβ: −0.025 [95% CI: −0.047, −0.004], p = 0.025; PCV2 aβ: −0.026 [95% CI: −0.048, −0.003], p = 0.028; PCV3 aβ: −0.026 [95% CI: −0.05, −0.002], p = 0.038). However, no associations were observed between PCV introduction or vaccination coverage and antibiotic consumption. Similarly, no associations were found between PCV coverage and the risk difference of either outcome. There was also no evidence of an association between PCV and the under-five mortality rate. No effect modification was observed by age group or baseline ARI prevalence.

Conclusion

At the population level, PCV introduction was associated with a reduction in ARI prevalence. Although antibiotic consumption appeared to decrease following PCV introduction, this reduction was not evident in the adjusted model estimates. Similarly, PCV introduction was not associated with changes in the under-five mortality rate. PCV may contribute to reductions in all-cause ARI through interactions between bacterial and viral respiratory pathogens, although the mechanisms underlying these broader effects remain an area of ongoing investigation. The relatively modest magnitude of the observed reduction in ARI, together with the lack of a significant association with antibiotic use, may be explained by several factors. These include potential serotype replacement, limitations of caregiver-reported recall data without etiological confirmation, low coverage, and other contextual factors that were not captured in this analysis. Nonetheless, in many resource-limited settings where pathogen-specific diagnostic data are not routinely available, nationally representative survey data provide one of the most feasible approaches for approximating population-level ARI burden across multiple countries. Overall, these findings suggest a potential population-level

effect of PCV on ARI burden while highlighting the need for longitudinal studies incorporating laboratory-confirmed outcomes to more precisely estimate vaccine impact where feasible.

4.1 Introduction

Acute respiratory infections (ARIs) remain a leading cause of morbidity and mortality among children under five globally, with the greatest burden in low- and middle-income countries (LMICs). (177) Globally, ARIs are responsible for 15-20% of all deaths among children under five years old. (178, 179) ARIs are attributable to multiple viral and bacterial pathogens, such as influenza virus, pertussis, respiratory syncytial virus (RSV), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. (180-182) ARIs are classified as upper respiratory infections (URIs), typically characterized by cough and inflammation of the nasal, pharyngeal, or laryngeal mucosa, or lower respiratory infections (LRIs), such as pneumonia and bronchitis, which are associated with greater severity. (182) Among bacterial causes of LRIs, *Streptococcus pneumoniae* (pneumococcus) remains a leading contributor to morbidity and mortality, with an estimated 344 million incident LRI episodes and 2.18 million LRI-attributable deaths in 2021. (183) In addition to pneumonia, pneumococcus can cause a range of illnesses, including otitis media, sinusitis, meningitis, and invasive bloodstream infections. (182) To reduce pneumococcal disease burden, pneumococcal conjugate vaccines (PCVs) were first introduced in 2000 and have been since incorporated into childhood immunization programs worldwide. (184) There are several PCV immunization schedules currently in use. While the three-dose primary schedule (3p+0) remains common in many LMICs, several high-income countries have transitioned to reduced-dose schedules. (185-188)

The global target for PCV coverage is 90% by 2030. (189) Despite this goal, coverage of the final PCV dose was only 51% globally in 2021, and as of January 2023,

39 countries had not fully integrated PCV into their national immunization programs. (189, 190) Although barriers to PCV introduction vary across settings, common challenges include limited sustainable financing, competing health priorities, constraints in vaccine delivery infrastructure and human resources, and weak disease surveillance systems. (190-192) Sustained financing and programmatic support for PCV implementation underscore the need for robust evidence to justify continued investment and scale-up, but such evidence remains limited. Moreover, pneumococcal etiology is difficult to ascertain in routine surveillance due to constrained diagnostic capacity and the infrequent isolation of pneumococcus. (193, 194) These limitations additionally complicate antibiotic stewardship efforts as few tools are available to confirm the etiology of ARIs and the treatment decisions are frequently based on clinical suspicion (195, 196) While vaccines are hypothesized to mitigate AMR by reducing infections that lead to antibiotic consumption, evidence supporting this effect remains scarce. (195, 197)

Beyond their role in preventing pneumococcal disease, PCV may also influence the risk of ARIs more broadly. For instance, Le et al. (2023) reported lower respiratory syncytial virus (RSV)–related hospitalization rates among infants receiving higher PCV doses (198), while Mechita et al. (2020) observed declines in childhood respiratory mortality in Morocco following PCV introduction. (199) In contrast, Lewnard et al. (2023) found no evidence of PCV13 effectiveness against RSV or adenoviruses and reported weaker protection against non-pneumonia lower respiratory tract infections. (195) Similarly, in a large adult PCV13 trial, Huijts et al. (2018) observed modest effectiveness against virus-associated pneumonia. (200) Taken together, the evidence on broader, non-pneumococcal effects of PCV on ARI remains inconsistent, highlighting an

important gap in the literature regarding the population-level impact of PCV on respiratory infections regardless of pathogen etiology.

Collectively, these findings indicate that additional investigation of the role of PCV in pediatric respiratory illness in LMICs is needed to better characterize potential population level effects, particularly in contexts where vaccine coverage varies over time and respiratory illness surveillance remains limited. Thus, this study aims to examine the impact of PCV on country-level ARI prevalence and antibiotic use during ARI episodes among young children in LMICs. As a secondary objective, we also evaluated PCV association with under-five mortality rates.

4.2 Methods

Data Source

This study utilizes data from the Demographic and Health Surveys (DHS) (201) and the Multiple Indicator Cluster Surveys (MICS) (202), two large-scale, nationally representative household survey programs conducted across low- and middle-income countries. Both surveys employ multistage, stratified sampling designs. Within each country, primary sampling units (PSUs) are selected from census-based sampling frames, stratified by geographic region and typically selected with probability proportional to size. Households within selected clusters are then randomly sampled and interviewed at intervals of approximately three to ten years. (203-205) DHS surveys generally include around 15,000 households per round, while MICS surveys include approximately 10,000. Both DHS and MICS collect detailed information on childhood immunization coverage, acute illnesses experienced in the two weeks preceding the survey, and key socioeconomic and household characteristics. (203-205)

Inclusion criteria

In this study, we restricted our analysis to countries with nationwide PCV implementation to ensure consistent interpretation of vaccine effects. Given that primary PCV doses are typically administered by 6 months of age, we included children aged 6 to 35 months. Children older than 35 months were excluded due to limited availability of comparable data across surveys. All post-PCV surveys were included for each country. When available, the pre-PCV survey conducted closest to the year of PCV introduction was selected.

Primary exposure

The primary exposures were the PCV introduction and PCV coverages. For the surveys prior PCV vaccination status was defined based on documentation of receipt of the first, second, and third doses recorded on vaccination cards or other official records. In the MICS, vaccination status was determined using recorded vaccination dates. Children were classified as having received a given PCV dose if a corresponding calendar date was available. PCV coverages were calculated as the proportion of children who received the respective vaccine doses, divided by the total number of children within each survey–year pair. PCV introduction was defined as a binary variable indicating whether a country had implemented PCV in its national immunization program by the survey year. Information on the year of PCV introduction was obtained from the WHO. (206)

Primary and secondary outcomes

The primary outcomes of this study include prevalences of ARI and antibiotic consumption during the episodes of ARI. In 2004, during the United Nations Children's

Fund (UNICEF)/World Health Organization (WHO) meeting on Child survival Survey-based Indicators, the use of the term ARI was recommended to reflect respiratory illness including presumed pneumonia, due to difficulty in making accurate diagnosis based on symptoms collected in the field. (207) For this study, we will use the UNICEF definition of ARI, which is "mothers' perceptions of a child who has a cough, is breathing faster than usual with short, quick breaths or is having difficulty breathing, excluding children that had only a blocked nose". (208) Antibiotic use was defined as mother-reported receipt of antibiotics for fever or cough during an episode of ARI in the two weeks preceding the survey. Although some survey instruments indicate that antibiotics were given for ARI treatment, we cannot confirm that antibiotic use was exclusively attributable to the respiratory infection, as fever and cough may co-occur with other conditions or be treated empirically in the absence of confirmed etiology. To assess the specificity of observed associations and address potential residual confounding, we additionally examined antibiotic use during diarrheal episodes as a negative control outcome. For both ARI and antibiotic use, prevalence was calculated as the proportion of children with the outcome divided by the total number of children within each survey–year pair. Lastly, as the secondary outcome, the under-five mortality rates for the five years preceding each survey where available, were extracted from each survey. All rates are expressed as deaths per 1,000 live births.

Covariates

Country-level characteristics were recoded for analysis. To account for household air pollution exposure, socioeconomic conditions, and healthcare access and utilization at the population level, the study included primary cooking fuel (as a proxy for household

air pollution), maternal education level, Diphtheria–Tetanus–Pertussis (DTP)/Pentavalent vaccination status, and source of care sought for acute respiratory infection. Households were classified as using solid fuel if the reported primary cooking fuel was coal, charcoal, wood, straw, shrubs or grass, crop residues, animal dung, or other solid fuels. Maternal education was categorized as primary or less if the mother reported no formal education or only primary-level education. The two education categories were combined to ensure cross-survey comparability, given inconsistencies in reporting across surveys. Receipt of at least one dose of the DTP or pentavalent vaccine was determined using vaccination card records, applying the same documentation-based approach used to define PCV vaccination. This variable was included as it serves as a key indicator of national immunization system performance. (209) Source of care for ARI was classified as public if the child received care from public-sector providers, including government hospitals, government health centers, or other facilities reported as part of the public sector. Lastly, time since PCV introduction was calculated for each country as the difference between the year of PCV introduction and the survey year.

Statistical Analysis

Variables were weighted using survey-specific sampling weights corresponding to each survey round. Aggregated estimates therefore reflect weighted population counts of children for each survey–year pair. All weighted estimates were cross-checked against the corresponding DHS and MICS reports to ensure consistency with published summary statistics. Prevalence ratios (PR) of ARI and antibiotic consumption were calculated to compare prevalence before and after PCV implementation, stratified by age and country income group. Country income classification was obtained from the World Bank and

categorized according to each country's status in the pre-PCV year. (210) Linear regression was used to estimate absolute changes in outcome prevalence and risk difference associated with PCV introduction and increasing coverage across dose levels. Quasi-Poisson models were used to estimate relative changes in prevalence associated with PCV introduction. Variance inflation factors (VIFs) were examined to assess multicollinearity among covariates. As observations were clustered within countries across survey-year pairs, robust standard errors clustered at the country level were used to account for within-country. Subgroup analyses were conducted stratified by age group, country income group, and baseline ARI prevalence level. Effect modification was assessed by including interaction terms in the regression models and evaluating them using Wald tests.

4.3 Results

We included 97 surveys conducted between 2005 and 2023 across 40 countries with universal PCV implementation. A total of 609,701children were included. At the time of pre-PCV year, 25 were classified as low-income, 11 as lower-middle-income, and 4 as upper-middle-income. By WHO region, 24 countries were in the Africa Region, followed by 5 in the Western Pacific Region, 4 in the Region of the Americas, 3 in the Eastern Mediterranean Region, and 2 countries each in the European and South-East Asia Regions (**Table 8**). The mean duration since PCV introduction was 3.8 ± 3.7 years. Currently, 33 countries use PCV13, of which 7 transitioned from either PCV7 or PCV10. In addition, six countries currently implement a 2p+1 schedule, whereas the majority (n = 34) maintain a three-primary-dose schedule (3p+0). (**Table 8**).

Across countries, ARI prevalence declined from 8.2% in the pre-PCV period to

5.8% post-PCV (PR: 0.7 [95% CI: 0.69, 0.72], p < 0.001), and antibiotic use decreased from 3.4% to 2.7% (PR: 0.78 [95% CI: 0.75, 0.81], p < 0.001). Among children with ARI, the prevalence of antibiotic use exceeded 40%. (**Table 9**) Reductions were observed across all age groups, with the largest relative declines among children aged 6–11 months for both ARI (PR: 0.67 [95% CI: 0.65, 0.7], p < 0.001) and antibiotic use (PR: 0.75 [95% CI: 0.71, 0.79], p < 0.001). By income group, the largest reductions occurred in upper-middle-income countries for ARI (PR: 0.45 [95% CI: 0.4–0.52], p < 0.001) and antibiotic use (PR: 0.43 [95% CI: 0.35–0.52], p < 0.001) (**Table 9**).

Figure 4 present the mean PCV coverages across the available survey years. PCV coverage increased over time, with some fluctuations, until 2019, after which coverage for all doses began to decline. The highest average coverage was observed in 2019, with PCV1 and PCV2 exceeding 70% and PCV3 approaching 70%. In 2013, the earliest survey year, coverage levels were lower, with PCV1 and PCV2 slightly above 50% and PCV3 below 50%. (**Figure 1, Appendix C. Supplementary Table 6**)

Across all countries, PCV introduction was associated with a 1.7 percentage point reduction in ARI prevalence (aβ: −0.017 [95% CI: −0.029, −0.005], p = 0.01) and a 24% lower ARI prevalence (aPR: 0.76 [95% CI: 0.646, 0.901], p = 0.002) compared with the pre-PCV period. No association was observed between PCV introduction and antibiotic use during ARI episodes. The negative control outcome analysis also supported this finding. (**Appendix C. Supplementary Table 7**) No effect modifications were observed. (**Table 10**)

An increase in PCV1, PCV2, and PCV3 coverage from 0 to 1 (0–100%) was associated with a 2.5 percentage-point reduction in ARI prevalence for each dose (PCV1

aβ: −0.025 [95% CI: −0.047, −0.004], p = 0.025; PCV2 aβ: −0.026 [95% CI: −0.048, −0.003], p = 0.028; PCV3 aβ: −0.026 [95% CI: −0.05, −0.002], p = 0.038). Although modest decreases in antibiotic use were observed with increasing PCV coverage, the associations were not statistically significant (PCV1 aβ: −0.003, 95% CI: −0.015, 0.01; p = 0.59; PCV2 aβ: −0.003, 95% CI: −0.016, 0.01; p = 0.473; PCV3 aβ: −0.004, 95% CI: −0.018, 0.011; p = 0.484). This was also confirmed by our negative outcome analysis. (**Appendix C. Supplementary Table 8**) No effect modifications were observed. (**Table 11**)

Small increases in the risk difference of ARI between the pre- and post-PCV eras were observed with increasing PCV coverage, but none of the associations were statistically significant (PCV1 aβ: 0.02 [95% CI: −0.069, 0.109], p = 0.507; PCV2 aβ: 0.017 [95% CI: −0.065, 0.099]. p = 0.538; PCV3 aβ: 0.028 [95% CI: −0.054, 0.11], p = 0.378). Similarly, small increases in the risk difference of antibiotic use were observed, but the associations were not statistically significant (PCV1 aβ: 0.005 [95% CI: −0.072, 0.083], p = 0.825; PCV2 aβ: 0.005 [95% CI: −0.069, 0.079], p = 0.84; PCV3 aβ: 0.013 [95% CI: −0.068, 0.093], p = 0.673). Findings from the negative control outcome analysis were consistent with these results. (**Appendix C. Supplementary Table 8**) No evidence of effect modification was observed. (**Table 12**)

PCV introduction was not associated with under-five mortality (aβ: 0.015 [95% CI: −0.055, 0.086], p = 0.654). Similarly, no associations were observed with increasing PCV coverage (PCV1 aβ: 0.016 [95% CI: −0.057, 0.09], p = 0.643; PCV2 aβ: 0.016 [95% CI: −0.057, 0.088], p = 0.656; PCV3 aβ: 0.014 [95% CI: −0.061, 0.089], p = 0.695). No effect modification was observed. (**Table 13**)

4.4 Discussion

In this study, we aggregated country-level datasets from DHS and MICS surveys conducted between 2005 and 2023. Most countries retained their initial PCV formulation over time, with more than 80% using PCV13 as the current product. Nearly all countries included in this analysis (95%) introduced PCV in 2012 or later, and approximately 30% implemented PCV in 2012. Overall PCV coverage increased gradually during the study period with fluctuations. However, beginning in 2019, coverage levels began to decline. Following PCV introduction, we observed reductions in the prevalence of ARI and antibiotic use. The decline in ARI prevalence remained evident in association with the introduction and the PCV coverage, and there was no difference in the reduction estimate between the first, second, third doses. Although not significant, we did also observe the declining trends of antibiotic consumption in association with increasing PCV coverages. PCV was not associated with under-five mortality rate. We did not observe evidence of effect modification by age group or income group for any of the outcomes examined.

The reduction in ARI prevalence observed in our study is consistent with prior evidence. Acute respiratory infections comprise both viral and bacterial etiologies. Previous studies have demonstrated that PCVs are effective in reducing vaccine-type pneumococcal carriage and associated morbidity (211-214). There is also evidence that PCV vaccination may also reduce broader ARI outcomes not directly attributable to vaccine-targeted pneumococcal serotypes. In a prospective cohort study conducted in Israel, Dagan et al. (2026) reported substantial declines in both incidence and hospitalization rates of respiratory syncytial virus–positive, community-acquired alveolar pneumonia (RSV-CAAP) following implementation of PCV13, with particularly

pronounced reductions among children aged 12–23 months. (215) Similarly, Le et al. (2023) observed that receipt of three or more PCV doses during the universally funded period was associated with an approximately 30% reduction in RSV-related hospitalizations among Aboriginal infants. (198) A randomized, placebo-controlled trial conducted in South Africa demonstrated that the PCV9 reduced pneumonia associated with respiratory viruses by 31% among hospitalized children without HIV infection. The study found protection against pneumonia cases linked to several respiratory viruses, including human parainfluenza viruses types 1–3, RSV, influenza A virus, and adenovirus, among children who received PCV9 at 6, 10, and 14 weeks of age. (216)

One possible explanation for the overall reduction relates to interactions between viral and bacterial pathogens, although the precise mechanisms remain incompletely understood. Growing evidence suggests that pneumococcal colonization can influence host immune responses during viral infection. For example, an experimental study has shown that induced pneumococcal carriage can attenuate mucosal antibody responses to live attenuated influenza vaccine, indicating that the presence of *Streptococcus pneumoniae* in the nasopharynx may modify antiviral immunogenicity. (217) Similar observation has been reported in the context of SARS-CoV-2 infection, where pneumococcal colonization has been associated with diminished antiviral immune responses. (218) At the same time, viral infections may increase pneumococcal colonization density, potentially heightening the risk of subsequent respiratory tract infections in children. (219) A prospective cohort study conducted in Peru among children younger than three years found that nasopharyngeal bacterial density, including *Streptococcus pneumoniae*, increased during episodes of viral acute respiratory illness,

suggesting that viral infections may promote bacterial proliferation and contribute to respiratory disease severity (220) Together, these findings suggest a bidirectional relationship in which viral and pneumococcal pathogens may amplify one another's effects. Within this framework, pneumococcal conjugate vaccines could reduce the risk or severity of viral lower respiratory tract infections if pneumococcus contributes to the broader causal pathway of viral respiratory disease. However, further investigation is needed to clarify this potential mechanism.

Although the direction of the association suggested a reduction, the effect of PCV on ARI prevalence, and particularly on antibiotic consumption, was modest. Several contextual factors may influence the observed impact following PCV introduction. One possible explanation is serotype replacement**,** which is the expansion of non-vaccine serotypes (NVTs) following declines in vaccine-type strains. As vaccine-targeted serotypes decrease, ecological niches in the nasopharynx become available, allowing NVTs to increase in colonization and, in some settings, sustain a residual burden of pneumococcal disease. Accumulating evidence suggests increasing serotype replacement, with rising incidence of non-vaccine-type invasive pneumococcal disease across multiple age groups (195, 221-223), which may partially offset the overall population-level benefits of vaccination. In parallel, inappropriate antibiotic use remains widespread in many LMIC settings. Aetiologic studies indicate that a substantial proportion of antibiotics administered for childhood ARI and diarrheal illness are unnecessary. For example, Fink et al. (2020) reported that up to 80% of children under five presenting to health facilities with ARI received antibiotics, often without a clear bacterial indication. (224) Multicountry analyses also show that non-prescription antibiotic use among young

children is substantially more common in low- and lower-middle-income countries than in higher-income settings. (225, 226) The high baseline level of antibiotic use in these settings may therefore attenuate observable reductions in antibiotic consumption following PCV introduction. Another key observation was that the effect of PCV did not differ meaningfully across doses. The emerging immunogenicity studies suggest that post-booster immune responses under a 1p+1 schedule may be equivalent or even superior to those achieved under the World Health Organization (WHO)–recommended three-dose schedules. (186, 187) Taken together with our findings, these results raise the possibility that a full three-dose primary series may not be necessary in some LMIC settings. However, this interpretation should be made cautiously and warrants further investigation, including robust cost-effectiveness analyses and evaluations of long-term population-level impact.

The lack of a measurable effect in this study may also reflect the time required for immunization programs to reach maturity after vaccine introduction. Although this timeline varies across countries, previous studies suggest that approximately 5 to 7 years are typically needed for vaccination coverage and population-level impacts to stabilize following the introduction of a new vaccine. (227, 228) Quesada et al. (2021) reported that in countries without catch-up campaigns or prior use of another PCV product, the mature phase of the immunization program was reached after seven years of continuous and exclusive use of PCV10 or PCV13, including the year of introduction (79). In our dataset, 21 countries had surveys conducted within five years of PCV introduction, which may have limited the ability to detect the full programmatic impact. Although indirect protection through herd immunity may begin to emerge within 1 to 2 years after vaccine

introduction, most evidence for this effect comes from community-level studies (229, 230) and may not necessarily translate into detectable changes at the national level. Importantly, PCV coverage of approximately 75% or higher may be required to achieve around 90% protection against pneumococcal disease at the population level. (213, 231) However, the average coverage observed in our study was below the suggested threshold. Taken together, these considerations may help explain the relatively modest magnitude of the effect observed in our analysis.

In our analysis, PCV coverage did not surpass 80% during the study period. Coverage reached its highest level in 2019 but subsequently declined, likely reflecting disruptions associated with the COVID-19 pandemic and has not returned to pre-pandemic levels. Even prior to 2019, coverage generally remained below 70% and fluctuated across survey years. Although gradual increases were observed over time, gains were modest and fell short of global immunization targets, including those aligned with the Sustainable Development Goals. (189) Beyond epidemiologic considerations, financial constraints remain central to both vaccine introduction and long-term program sustainability. Decisions to adopt and maintain newer vaccines within national Expanded Programs on Immunization (EPI) depend not only on cost-effectiveness evidence but also on vaccine price, affordability, and predictable financing mechanisms. Unlike long-established childhood vaccines, pneumococcal conjugate vaccines represent a substantial share of immunization program costs. (232, 233) The expanding share of immunization budgets devoted to newer vaccines underscores the importance of sustainable financing strategies to maintain coverage gains over time.

It is important to recognize several limitations inherent to the use of Demographic

and Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS) data. In these surveys, antibiotic use is measured based on caregiver recall of medications administered to children with symptoms such as fever and cough within the preceding two weeks. Because the surveys do not consistently collect information on the underlying clinical diagnosis, laboratory confirmation, or the specific indication for antibiotic treatment, we intentionally avoid referring to the outcome as "antibiotic-treated ARI," which would imply diagnostic certainty and clinical appropriateness. Instead, the measure is more accurately described as reported antibiotic use among children with respiratory symptoms. In addition, the estimates may be subject to recall bias, as caregivers are asked to recall symptoms and treatments over the preceding two weeks, which may lead to misclassification due to imperfect recall or differences in symptom recognition. (234) Second, respiratory symptoms are inherently nonspecific. The ARI indicator therefore likely captures a heterogeneous group of conditions that vary substantially in etiology, severity, and clinical significance. Consequently, the outcome measure reflects reported respiratory symptoms rather than clinically confirmed disease, and the estimates should be interpreted accordingly. Third, surveys were conducted at discrete time points and represent repeated cross-sectional data rather than continuous follow-up. As such, we are unable to fully characterize secular trends in associations over time. This limitation is particularly relevant in the context of vaccination coverage, which may be influenced by evolving economic conditions, disease outbreaks, health system changes, and national immunization policies. The absence of longitudinal data restricts our ability to assess within-country trajectories or short-term fluctuations surrounding vaccine introduction and scale-up, particularly in relation to changes in ARI burden. Finally, although we

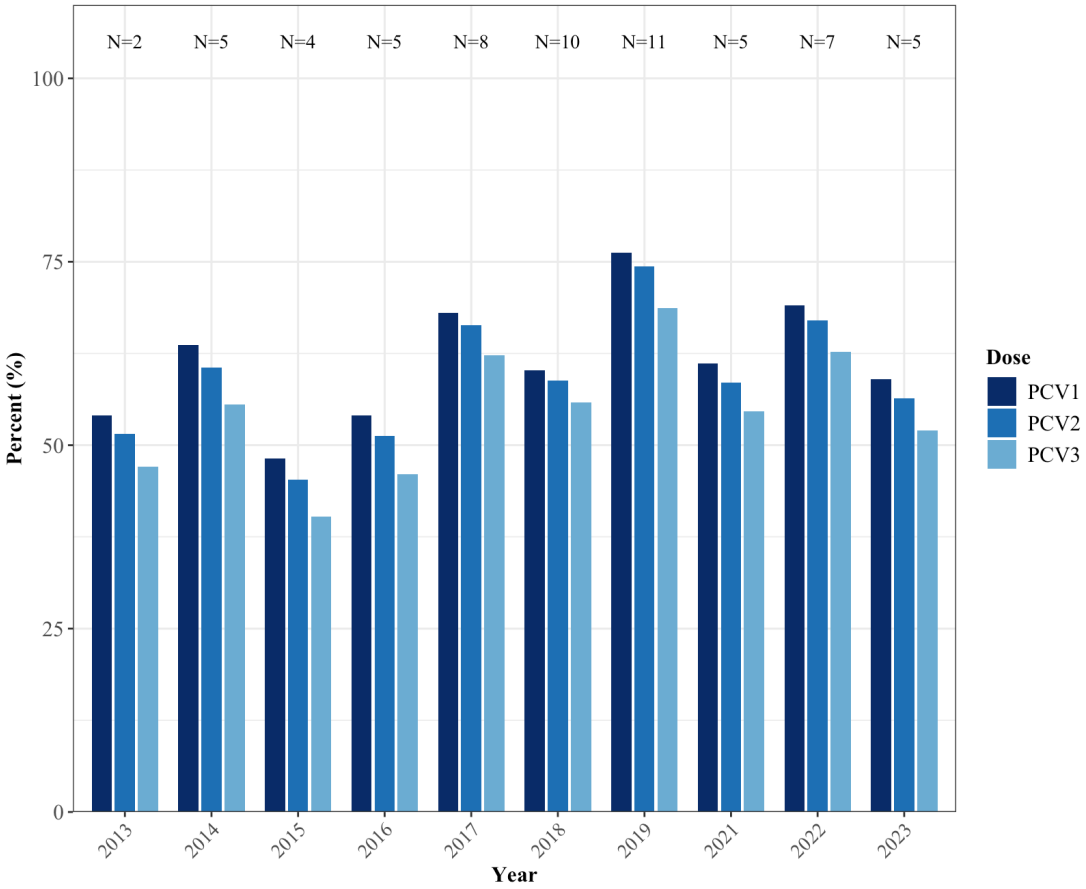
adjusted for a range of theoretically and empirically relevant covariates to reduce confounding, residual confounding and unmeasured heterogeneity across countries and survey waves likely remain. Differences in healthcare infrastructure, prescribing practices, antimicrobial stewardship, and broader structural determinants may influence both symptom reporting and antibiotic use in ways that cannot be fully captured in survey-based analyses.

Despite the known limitations of the reported ARI indicator, the measure remains widely used and methodologically valuable in population-based research. The ARI indicator in DHS and MICS surveys was developed as a pragmatic and standardized measure to approximate symptom-defined respiratory illness. Its straightforward structure enables consistent application across LMICs, facilitating cross-country comparability in large-scale surveys. Although the indicator lacks diagnostic specificity, it provides valuable insight into population-level patterns of respiratory symptoms and related healthcare use. In contexts where laboratory confirmation and routine clinical verification are not widely available, such standardized symptom-based measures remain essential for assessing the burden of respiratory illness at scale. Furthermore, the large sample sizes of surveys confer substantial statistical power, allowing for precise estimation of prevalence and associations across subgroups. Taken together, while the ARI indicator is imperfect and should not be interpreted as a direct measure of clinically confirmed pneumonia, it remains a valuable and practical proxy for assessing respiratory symptom burden and related treatment patterns in settings where alternative surveillance systems are limited or unavailable.

This addresses an important gap in the literature, as comprehensive evaluations of

the population-level impact of pneumococcal conjugate vaccine across diverse settings remain limited. By leveraging nationally representative survey data from multiple countries, we provide a broad assessment of PCV coverage patterns and their association with respiratory symptoms and antibiotic use. In doing so, this work offers a consolidated overview of PCV implementation progress and its potential public health implications in low- and middle-income countries. Future research should aim to strengthen causal interpretation by linking population-based survey data with laboratory-confirmed pneumococcal disease surveillance systems. Such integration would help disentangle pathogen-specific vaccine effects from broader respiratory outcomes and clarify the mechanisms underlying observed associations. Additionally, longitudinal cohort studies are needed to better characterize the temporal relationships between vaccination, respiratory illness episodes, healthcare utilization, and antibiotic use. Together, these efforts would provide a more nuanced understanding of both the direct and indirect effects of PCV and further inform immunization policy and antimicrobial stewardship strategies.

Figure 4. Mean annual PCV coverages[1]



1. N = Number of countries

Table 8. Characteristics of national PCV programs across study countries (206, 235-259)

Country	Income group	WHO Region[1]	Universal PCV Introduction	Current PCV Schedule[2]	Initial PCV valence	PCV valence change	Current PCV valence
Afghanistan	Low	EMRO	2014	6,10,14 wks (3p+0)	PCV13	No	PCV13
Angola	Upper-middle	AFRO	2013	2,4, 6m (3p+0)	PCV13	No	PCV13
Albania	Lower-middle	EURO	2011	2,4,12 m (2p+1)	PCV10	Yes, 2018	PCV13
Armenia	Lower-middle	EURO	2014	6,12,18 wks (3p+0)	PCV10	Yes, 2016	PCV13
Bangladesh	Lower-middle	SEARO	2015	6,10,14 wks (3p+0)	PCV10	No	PCV10
Benin	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Burkina Faso	Low	AFRO	2013	2,4,9 m (2p+1)	PCV13	No	PCV13
Burundi	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Cambodia	Low	WPRO	2015	6,10,14 wks (3p+0)	PCV13	No	PCV13
Cameroon	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Central African Republic	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Côte d'Ivoire	Lower-middle	AFRO	2014	6,10,14 wks (3p+0)	PCV13	No	PCV13
Costa Rica	Upper-middle	AMRO	2008	2,4,15 m (2p+1)	PCV7	Yes, 2011	PCV13
Dominican Republic	Upper-middle	AMRO	2013	2,4,12 m (2p+1)	PCV13	No	PCV13
Ethiopia	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV10	Yes, 2020	PCV13
Fiji	Upper-middle	WPRO	2012	6,10,14 wks (3p+0)	PCV10	No	PCV10
Gambia	Low	AFRO	2009	2,3,4 m (3p+0)	PCV7	Yes, 2011	PCV13
Ghana	Low	AFRO	2012	6,10,14 wks (3p+0)	PCV13	No	PCV13
Guinea-Bissau	Low	AFRO	2015	6,10,14 wks (3p+0)	PCV13	No	PCV13
Guyana	Lower-middle	AMRO	2011	2,4,6 m (3p+0)	PCV7	Yes, 2011	PCV13
Honduras	Lower-middle	AMRO	2011	2,4,6m (3p+0)	PCV13	No	PCV13
Kenya	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV10	No	PCV10
Kiribati	Lower-middle	WPRO	2013	6,10,14 wks (3p+0)	PCV13	No	PCV13
Lao PDR	Lower-middle	WPRO	2013	6,10,14 wks (3p+0)	PCV13	No	PCV13
Lesotho	Lower-middle	AFRO	2015	6,10,14 wks (3p+0)	PCV13	No	PCV13

Liberia	Low	AFRO	2014	6,10,14 wks (3p+0)	PCV13	No	PCV13
Madagascar	Low	AFRO	2012	6,10,14 wks (3p+0)	PCV10	No	PCV10
Malawi	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Mali	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Nepal	Low	SEARO	2015	6,10 wks, 9m (2p+1)	PCV10	No	PCV10
Pakistan	Low	EMRO	2014	6,10,14 wks (3p+0)	PCV10	No	PCV13
Philippines	Lower-middle	WPRO	2020	6,10,14 wks (3p+0)	PCV10	Yes, 2014	PCV13
São Tomé & Príncipe	Lower-middle	AFRO	2012	6,10,14 wks (3p+0)	PCV13	No	PCV13
Senegal	Lower-middle	AFRO	2013	6,10,14 wks (3p+0)	PCV13	No	PCV13
Sierra Leone	Low	AFRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Togo	Low	AFRO	2014	6,10,14 wks (3p+0)	PCV13	No	PCV13
Uganda	Low	AFRO	2014	6,10,14 wks (3p+0)	PCV10	No	PCV10
Yemen	Low	EMRO	2011	6,10,14 wks (3p+0)	PCV13	No	PCV13
Zambia	Low	AFRO	2013	6,10,14 wks (3p+0)	PCV10	No	PCV10
Zimbabwe	Low	AFRO	2012	6,10,14 wks (3p+0)	PCV13	No	PCV13

1. AFRO: African Region, AMRO: Region of the Americas, EMRO: Eastern Mediterranean Region, EURO: European Region, SEARO: South-East Asia Region, WPRO: Western Pacific Region
2. 3p+0: 3 primary doses, 2p+1: 2 primary doses and 1 booster dose, wks: weeks, m: months

Table 9. Prevalence of ARI and antibiotic use during ARI before and after PCV introduction[1]

Group	PCV status	Total N	ARI N (%)	Abx use N (%)	Abx use among ARI N (%)	ARI PR[2] (95% CI)	Abx use PR[2] (95% CI)
Overall	Pre	131,558	10,813 (8.2%)	4,486 (3.4%)	4,486 (41.5%)	0.7 (0.69, 0.72)	0.78 (0.75, 0.81)
	Post	478,143	27,667 (5.8%)	12,724 (2.7%)	12,724 (46.0%)		
Age (months)							
6-11	Pre	52,269	4,380 (8.4%)	1,825 (3.5%)	1,825 (41.7%)	0.67 (0.65, 0.7)	0.75 (0.71, 0.79)
	Post	197,403	11,151 (5.6%)	5,188 (2.6%)	5,188 (46.5%)		
12-23	Pre	51,856	3,935 (7.6%)	1,601 (3.1%)	1,601 (40.7%)	0.73 (0.70, 0.75)	0.8 (0.75, 0.84)
	Post	189,167	10,427 (5.5%)	4,671 (2.5%)	4,671 (44.8%)		
24-35	Pre	27,433	2,498 (9.1%)	1,060 (3.9%)	1,060 (42.4%)	0.73 (0.7, 0.76)	0.81 (0.75, 0.87)
	Post	91,573	6,089 (6.6%)	2,865 (3.1%)	2,865 (47.1%)		
Income group							
Low	Pre	93,080	8,272 (8.9%)	3,440 (3.7%)	3,440 (41.6%)	0.81 (0.79, 0.83)	0.91 (0.87, 0.95)
	Post	206,660	14,875 (7.2%)	6,950 (3.4%)	6,950 (46.7%)		
Lower-middle	Pre	36,694	2,337 (6.4%)	946 (2.6%)	946 (40.5%)	0.46 (0.43, 0.49)	0.41 (0.37, 0.46)
	Post	56,867	1,668 (2.9%)	608 (1.1%)	608 (36.4%)		
Upper-middle	Pre	1,783	204 (11.5%)	101 (5.6%)	101 (49.2%)	0.45 (0.4, 0.52)	0.43 (0.35, 0.52)
	Post	214,617	11,124 (5.2%)	5,166 (2.4%)	5,166 (46.4%)		

1. PCV: Pneumococcal conjugate vaccine, Abx: Antibiotic, PR: Prevalence Ratio, m: months, N: Number of children

2. All p-values were < 0.001, except for the PR for antibiotic use in low-income countries, where the p-value was 0.01

Table 10. Association between PCV introduction and ARI and Antibiotic use[1-3]

Outcome	Acute Respiratory Infection (ARI)						
Group	**Level**	**aß (95% CI)**	**p-val[3]**	**p-val[4]**	**aPR (95% CI)**	**p-val**	**p-val[4]**
Overall	-	-0.017 (-0.029, -0.005)	0.01	-	0.76 (0.641, 0.901)	0.002	-
Age	6-11 m	-0.013 (-0.024, -0.003)	0.016	0.257	0.773 (0.667, 0.912)	0.002	0.863
	12-23 m	-0.016 (-0.026, -0.005)	0.007		0.759 (0.624, 0.916)	0.004	
	24-35 m	-0.015 (-0.03, -0.001)	0.034		0.726 (0.609, 0.864)	< 0.001	
Baseline ARI	< 5%	0.008 (-0.023, 0.039)	0.482	0.402	1.314 (0.662, 2.611)	0.435	0.429
	5-9%	-0.014 (-0.024, -0.005)	0.006		0.548 (0.454, 0.736)	< 0.001	
	≥10%	-0.037 (-0.216, 0.141)	0.4		0.831 (0.759, 0.909)	< 0.001	
Antibiotic use (Abx use)							
Group	**Level**	**aß (95% CI)**	**p-val**	**p-val[4]**	**aPR (95% CI)**	**p-val**	**p-val[4]**
Overall	-	0.001 (-0.006, 0.007)	0.854	-	0.958 (0.739, 1.243)	0.574	-
Age	6-11 m	0.002 (-0.004, 0.009)	0.456	0.426	0.915 (0.733, 1.144)	0.749	0.641
	12-23 m	0.0003 (-0.005, 0.006)	0.924		0.641 (0.451, 0.912)	0.013	
	24-35 m	-0.0002 (-0.01, 0.01)	0.962		0.9 (0.676, 1.199)	0.473	
Baseline ARI	< 5%	-0.003 (-0.017, 0.012)	0.634	0.924	0.996 (0.586, 1.694)	0.988	0.443
	5-9%	-0.0004 (-0.006, 0.005)	0.875		0.641 (0.451, 0.912)	0.013	
	≥10%	0.012 (-0.091, 0.114)	0.612		1.3 (1.085, 1.558)	< 0.001	

1. Analyses were limited to those countries with both pre- and post-PCV surveys
2. PCV: Pneumococcal conjugate vaccine, m; months
3. All models were adjusted for time since PCV introduction, urban residence, household solid fuel use, receipt of DTP/pentavalent vaccine, care seeking at a public health facility, maternal education, and country
4. p-value for interaction calculated using Wald test

Table 11. Association between PCV coverages and ARI and Antibiotic use[1,2]

Group	PCV	Level	Acute Respiratory Infection			Antibiotic use		
			aß (95% CI)	p-val	p-val[3]	aß (95% CI)	p-val	p-val[3]
Overall	PCV1	-	-0.025 (-0.047, -0.004)	0.025	-	-0.003 (-0.015, 0.01)	0.59	-
	PCV2	-	-0.026 (-0.048, -0.003)	0.028	-	-0.003 (-0.016, 0.01)	0.473	-
	PCV3	-	-0.026 (-0.05, -0.002)	0.038	-	-0.004 (-0.018, 0.011)	0.484	-
Age	PCV1	6-11 m	-0.021 (-0.041, -0.001)	0.03	0.287	-0.001 (-0.012, 0.01)	0.889	0.414
		12-23 m	-0.029 (-0.054, -0.003)	0.029		-0.005 (-0.019, 0.009)	0.486	
		24-35 m	-0.021 (-0.041, -0.001)	0.043		-0.001 (-0.016, 0.015)	0.943	
	PCV2	6-11 m	0.003 (-0.097, 0.103)	0.925	0.144	-0.024 (-0.085, 0.036)	0.248	0.245
		12-23 m	0.005 (-0.032, 0.043)	0.984		0.005 (-0.039, 0.049)	0.684	
		24-35 m	0.083 (-0.06, 0.226)	0.207		0.027 (-0.098, 0.151)	0.62	
	PCV3	6-11 m	0.006 (-0.105, 0.116)	0.881	0.05	-0.03 (-0.096, 0.036)	0.244	0.528
		12-23 m	-0.003 (-0.071, 0.065)	0.905		0.004 (-0.04, 0.047)	0.803	
		24-35 m	0.089 (-0.037, 0.214)	0.13		0.055 (-0.063, 0.173)	0.287	
Baseline ARI	PCV1	< 5%	0.022 (-0.03, 0.075)	0.256	0.742	-0.002 (-0.02, 0.015)	0.673	0.29
		5-9%	-0.016 (-0.035, 0.002)	0.07		0.001 (-0.008, 0.009)	0.822	
		≥10%	-0.076 (-0.791, 0.639)	0.51		-0.001 (-0.264, 0.261)	0.968	
	PCV2	< 5%	0.022 (-0.034, 0.078)	0.274	0.753	-0.002 (-0.021, 0.016)	0.683	0.426
		5-9%	-0.016 (-0.035, 0.003)	0.084		0.001(-0.008, 0.01)	0.790	
		≥10%	-0.075 (-0.904, 0.754)	0.536		-0.008 (-0.260, 0.243)	0.803	
	PCV3	< 5%	0.023 (-0.034, 0.081)	0.264	0.746	-0.002 (-0.023, 0.018)	0.722	0.491
		5-9%	-0.016 (-0.036, 0.005)	0.123		0.001 (-0.009, 0.01)	0.859	
		≥10%	-0.109 (-0.812, 0.594)	0.403		-0.033 (-0.221, 0.155)	0.363	

1. PCV: Pneumococcal conjugate vaccine, m; months
2. All models were adjusted for time since PCV introduction, urban residence, household solid fuel use, receipt of DTP/pentavalent vaccine, care seeking at a public health facility, maternal education, and country
3. p-value for interaction calculated using Wald test

Table 12. Association between PCV coverages and ARI and Antibiotic use risk differences[1-3]

Group	PCV	Level	Acute Respiratory Infection (ARI)			Antibiotic use (Abx use)		
			aRD (95% CI)	p-val	p-val[4]	aRD (95% CI)	p-val	p-val[4]
Overall	PCV1	-	0.02 (-0.069, 0.109)	0.507	-	0.005 (-0.072, 0.083)	0.825	-
	PCV2	-	0.017 (-0.065, 0.099)	0.538	-	0.005 (-0.069, 0.079)	0.84	-
	PCV3	-	0.028 (-0.054, 0.11)	0.378	-	0.013 (-0.068, 0.093)	0.673	-
Age	PCV1	6-11 m	0.007 (-0.113, 0.128)	0.816	0.271	-0.024 (-0.091, 0.044)	0.267	0.382
		12-23 m	0.002 (-0.078, 0.081)	0.941		0.006 (-0.042, 0.054)	0.656	
		24-35 m	0.074 (-0.072, 0.22)	0.237		0.03 (-0.115, 0.174)	0.602	
	PCV2	6-11 m	0.004 (-0.1, 0.108)	0.889	0.189	-0.024 (-0.087, 0.039)	0.265	0.405
		12-23 m	0.001 (-0.072, 0.074)	0.956		0.005 (-0.04, 0.05)	0.68	
		24-35 m	0.071 (-0.066, 0.208)	0.254		0.025 (-0.096, 0.147)	0.63	
	PCV3	6-11 m	0.007 (-0.103, 0.116)	0.856	0.094	-0.029 (-0.096, 0.038)	0.255	0.707
		12-23 m	-0.001 (-0.068, 0.066)	0.968		0.004 (-0.04, 0.048)	0.774	
		24-35 m	0.072 (-0.054, 0.198)	0.181		0.058 (-0.078, 0.193)	0.297	

1. PCV: Pneumococcal conjugate vaccine, RD: Risk difference, m; months
2. All models were adjusted for time since PCV introduction, urban residence, household solid fuel use, receipt of DTP/pentavalent vaccine, care seeking at a public health facility, maternal education, and country
3. Insufficient heterogeneity in risk differences by baseline ARI prevalence
4. p-value for interaction calculated using Wald test

Table 13. Association between PCV and mortality rate[1,2]

Exposure	PCV introduction				
Group	**Level**		**aß (95% CI)**	**p-val**	**p-val[3]**
Overall	-		0.015 (-0.055, 0.086)	0.654	
Age	6-11 m		0.014 (-0.056, 0.084)	0.679	0.6
	12-23 m		0.015 (-0.054, 0.084)	0.65	
	24-35 m		0.016 (-0.052, 0.083)	0.628	
Baseline ARI	< 5%		0.194 (-0.219, 0.607)	0.21	0.349
	5-9%		-0.035 (-0.056, -0.014)	0.834	
	≥10%		-0.003 (-0.08, 0.073)	0.004	
Exposure	**PCV coverages**				
Group	**PCV**	**Level**	**aß (95% CI)**	**p-val**	**p-val[2]**
Overall	PCV1	-	0.016 (-0.057, 0.09)	0.643	-
	PCV2	-	0.016 (-0.057, 0.088)	0.656	-
	PCV3	-	0.014 (-0.061, 0.089)	0.695	-
Age	PCV1	6-11 m	0.013 (-0.056, 0.081)	0.7	0.561
		12-23 m	0.019 (-0.051, 0.09)	0.578	
		24-35 m	0.01 (-0.044, 0.064)	0.712	
	PCV2	6-11 m	0.075 (-0.395, 0.544)	0.598	0.663
		12-23 m	-0.026 (-0.267, 0.216)	0.708	
		24-35 m	-0.043 (-0.299, 0.212)	0.695	
	PCV3	6-11 m	0.069 (-0.431, 0.569)	0.686	0.687
		12-23 m	-0.028 (-0.280, 0.224)	0.737	
		24-35 m	-0.083 (-0.622, 0.456)	0.71	
Baseline ARI	PCV1	< 5%	0.31 (-0.349, 0.97)	0.218	0.315
		5-9%	-0.043 (-0.083, -0.002)	0.041	
		≥10%	0.044 (-0.174, 0.263)	0.3	
	PCV2	< 5%	0.324 (-0.353, 1.002)	0.209	0.313
		5-9%	-0.042 (-0.083, -0.001)	0.048	
		≥10%	0.049 (-0.211, 0.309)	0.302	
	PCV3	< 5%	0.344 (-0.395, 1.082)	0.214	0.355
		5-9%	-0.042 (-0.083, -0.0001)	0.05	
		≥10%	0.055 (-0.317, 0.428)	0.416	

1. PCV: Pneumococcal conjugate vaccine, m; months
2. All models were adjusted for time since PCV introduction, urban residence, household solid fuel use, receipt of DTP/pentavalent vaccine, care seeking at a public health facility, maternal education, and country
3. p-value for interaction calculated using Wald test

5. 1 Summary of Findings

This dissertation examined the roles of environmental exposures and immunization in shaping respiratory health. By combining datasets from different countries and study designs, the analyses provide evidence from multiple contexts. The first two papers used data from a set of randomized trials conducted in rural Nepal. These trials included Trial 1, which evaluated the effect of the improved biomass stove Envirofit, and Trial 2, which compared the effects of two clean cooking technologies, Envirofit and liquefied petroleum gas (LPG) cookstoves. In the first paper, we found that in rural Nepalese communities where biomass cooking is common, the use of an improved biomass-burning stove modestly reduced the risk of respiratory infection among young children. Compared with Envirofit, LPG appeared to further reduce this risk, although the difference between the two technologies was not statistically significant. We also observed that the benefits of the intervention varied by contextual factors. In Trial 1, households that received stove installations during the winter experienced greater reductions in respiratory infections. In Trial 2, households with smokers appeared to benefit more from the LPG cookstove compared with households without smokers. Overall, these findings suggest that while clean cooking interventions provide modest improvements in children's respiratory morbidity, the magnitude of benefit may vary by season, additional sources of household air pollution exposure, and the type of clean cooking technology used.

The second paper focused on pulmonary function among individuals from the same study population but expanded the analysis to participants aged 10 years and older. In this study, pulmonary obstruction was defined as an FEV_1/FEV_6 ratio below 0.73, and

the analysis used data from Trial 1. We found that the use of cleaner cookstoves significantly reduced the risk of pulmonary obstruction. The effect was particularly pronounced among households with stove installations during the autumn and winter seasons, as well as among those with outdoor stove placement or chimney installations. These findings suggest that clean cooking can provide meaningful protection for pulmonary function. This benefit appears to be particularly pronounced during colder seasons, when fuel use is typically higher and indoor pollution levels may increase. The results also indicate that improved ventilation, together with cleaner cooking technologies, may further amplify these respiratory health benefits.

The final paper used pooled data from DHS and MICS across LMICs to evaluate the population-level impact of PCV introduction. The analysis showed that PCV introduction was associated with a reduction in ARI prevalence, and increasing PCV coverage was also associated with reductions in ARI burden. However, we did not observe a significant association between PCV introduction and antibiotic use, although modest declines in antibiotic consumption were observed with increasing coverage. No effect modification was detected in subgroup analyses. The annual mean PCV coverage across the surveys did not exceed 80%, and the average time since vaccine introduction was less than four years. Factors such as serotype replacement, high baseline antibiotic consumption, the time required for immunization programs to mature, and broader secular trends that were not fully accounted for may have influenced the magnitude of the observed effects. These findings suggest that while the overall reduction in ARI associated with PCV introduction is evident, further experimental and longitudinal studies are needed to better understand the vaccine's broader impact on respiratory illness

and antibiotic use.

5.2 Strengths and limitations

This dissertation provides empirical evidence on the health benefits of clean cooking interventions. By drawing on data from randomized trials, it examines respiratory outcomes across multiple age groups, from young children to older individuals, and across a spectrum of respiratory conditions ranging from suspected infections to pulmonary function. The findings from the first two papers contribute to an important gap in the literature by providing rigorous empirical evidence on the health impacts of clean cooking technologies. Despite a range of studies conducted since the initiation of these cookstove trials, the complexity of trial design and the substantial resources required for implementation have limited the availability of strong causal evidence. As a result, these analyses represent an important contribution to the ongoing effort to build robust evidence on the effectiveness of cleaner cooking interventions and to inform global clean cooking initiatives. In addition, the analyses examined whether intervention effects differed across population subgroups, providing insight into whether certain populations may benefit more from clean cooking interventions. This information is particularly relevant for policy decisions and the financing of large-scale interventions, as it may help identify priority populations and optimize resource allocation. The third paper also makes a unique contribution by using nationally representative surveys to conduct an ecological analysis of the population-level impact of PCV introduction. Few studies have used nationally representative survey data to examine the broader population-level effects of PCV on pediatric acute respiratory infections and antibiotic use. This analysis therefore provides complementary evidence on the broader public

health impact of PCV and offers a descriptive overview of PCV coverage trends across countries, thereby contributing to the current literature gap.

Several limitations should be acknowledged. First, in the cookstove trials, baseline levels of household air pollution remained substantially higher than the levels recommended by the World Health Organization. This likely reflects several factors, including intermittent continued use of traditional biomass stoves due to stove stacking, households' prior reliance on biomass fuels, and contributions from neighborhood-level air pollution. As a result, although the clean cookstove interventions effectively reduced household air pollution, the magnitude of the health benefits observed may have been attenuated. This limitation is particularly relevant because the trials were conducted in real-world community settings rather than under tightly controlled experimental conditions. Second, the survey-based analyses relied on cross-sectional data and caregiver recall, which may introduce recall bias and limit causal interpretation. Additionally, although the analyses adjusted, there may still be residual confounding from factors that could not be fully measured or controlled. Finally, the measure of antibiotic use was non-specific, as the surveys did not capture the clinical indication for treatment. Therefore, it cannot be definitively determined whether the reported antibiotic use was prescribed specifically for acute respiratory infections or for other conditions. Although robustness checks using a negative control outcome were conducted, the potential for misclassification cannot be completely ruled out.

5.3 Conclusion

Global efforts to improve respiratory health and protect populations from a wide range of infectious and environmental threats require effective and sustainable interventions. However, the successful development, implementation, and scaling of such interventions depend on the availability of robust and contextually relevant evidence. Policymakers and public health practitioners rely on rigorous data to guide resource allocation, financing decisions, and the prioritization of interventions that can deliver the greatest health benefits. Generating this evidence requires examining health outcomes from multiple perspectives and across diverse populations, using a variety of data sources and study designs.

This dissertation contributes to these efforts by examining respiratory health through both environmental and immunization-related pathways. By leveraging randomized trial data alongside nationally representative survey data from multiple countries, the analyses presented here provide evidence across different populations, age groups, and methodological approaches. Although each analysis has its limitations, together they offer complementary insights into how interventions such as clean cooking technologies and pneumococcal vaccination can influence respiratory outcomes. These findings help fill important gaps in the literature and contribute to the growing body of evidence supporting interventions that address both environmental exposures and infectious disease prevention.

Respiratory health is shaped by complex and interconnected biological, environmental, and structural factors. As a result, no single intervention or dataset can fully capture the range of determinants influencing respiratory outcomes. Continued

research using diverse methodologies, longer follow-up periods, and broader geographic representation will therefore remain essential. Strengthening the evidence base through sustained investigation will help guide more effective public health strategies aimed at reducing respiratory disease burden and improving population health worldwide.

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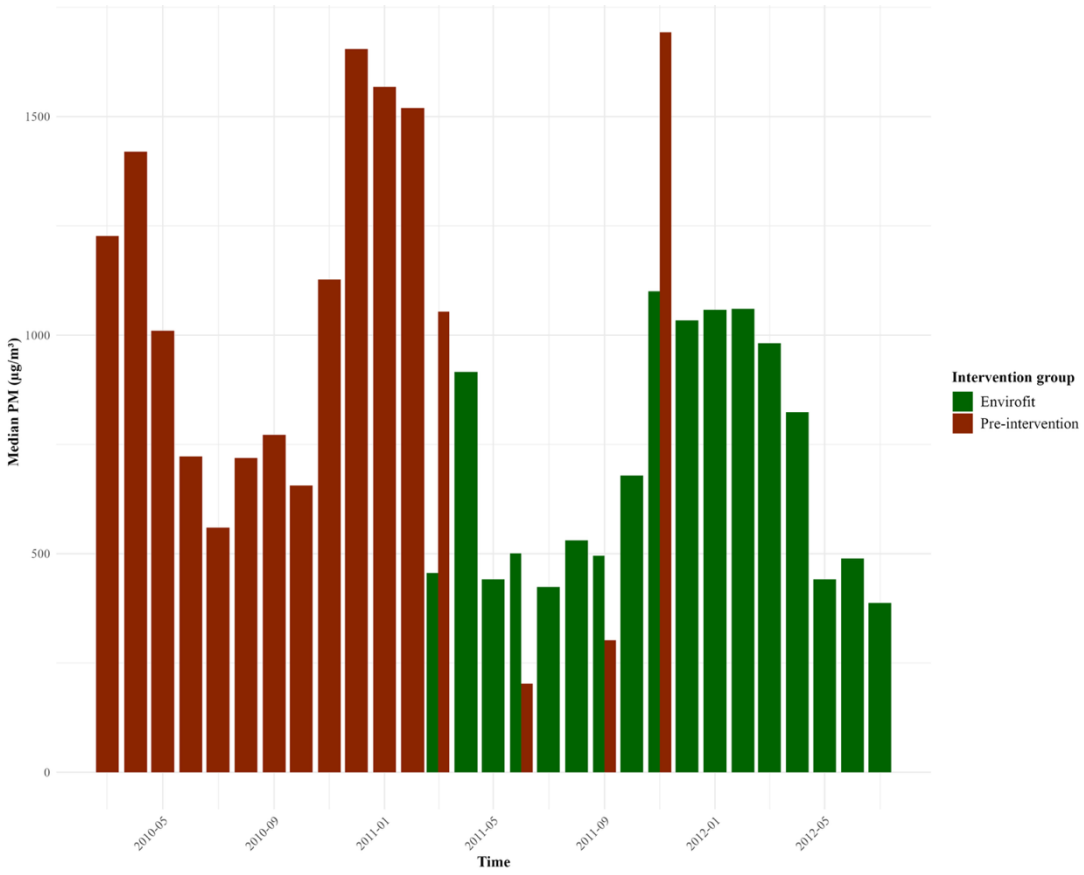
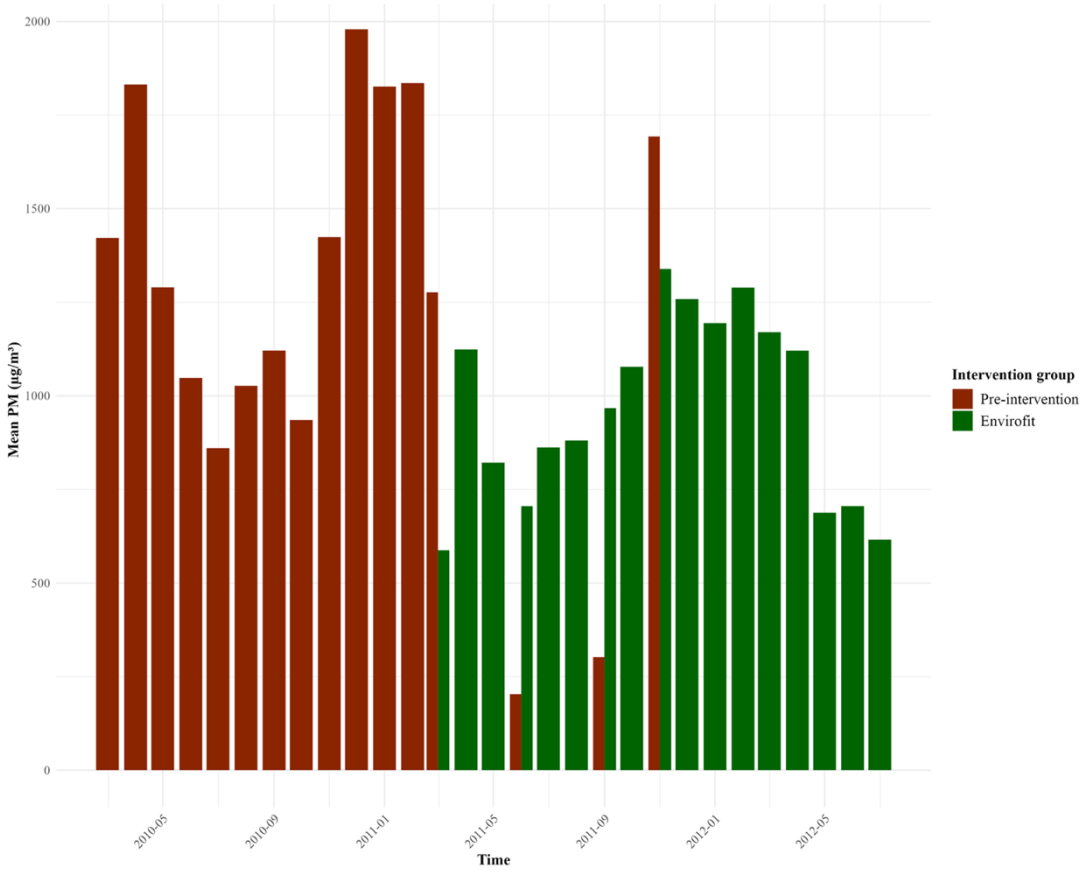
Appendix A. Chapter 2 Supplementary Figures and Tables

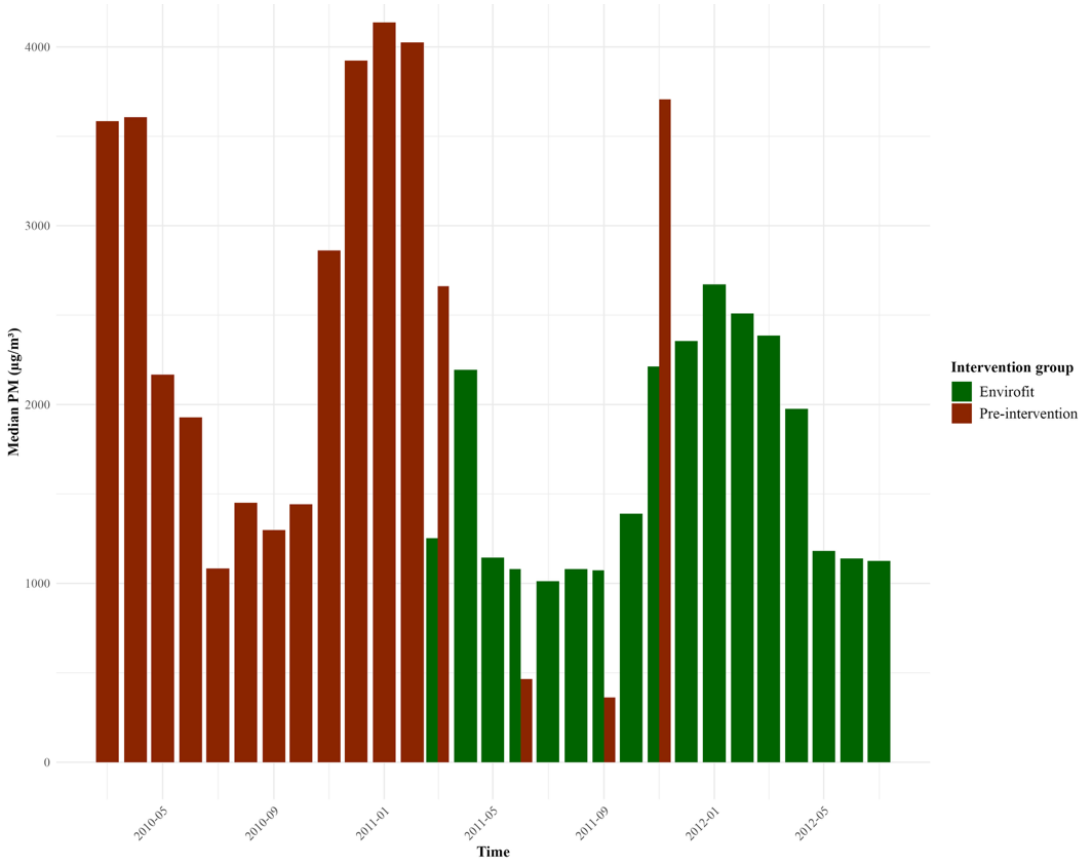
Supplementary Figure 1. Median PM concentration overtime in Trial 1



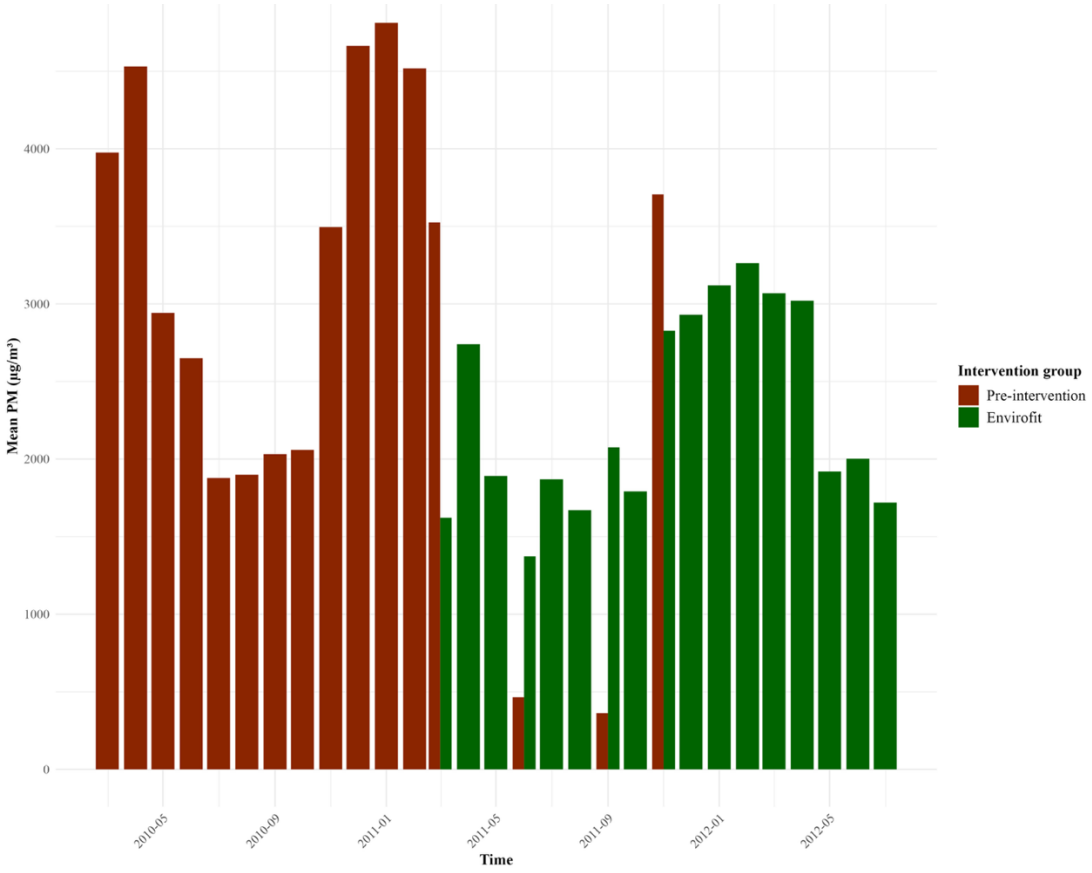
Supplementary Figure 2. Mean overall PM concentration in Trial 1



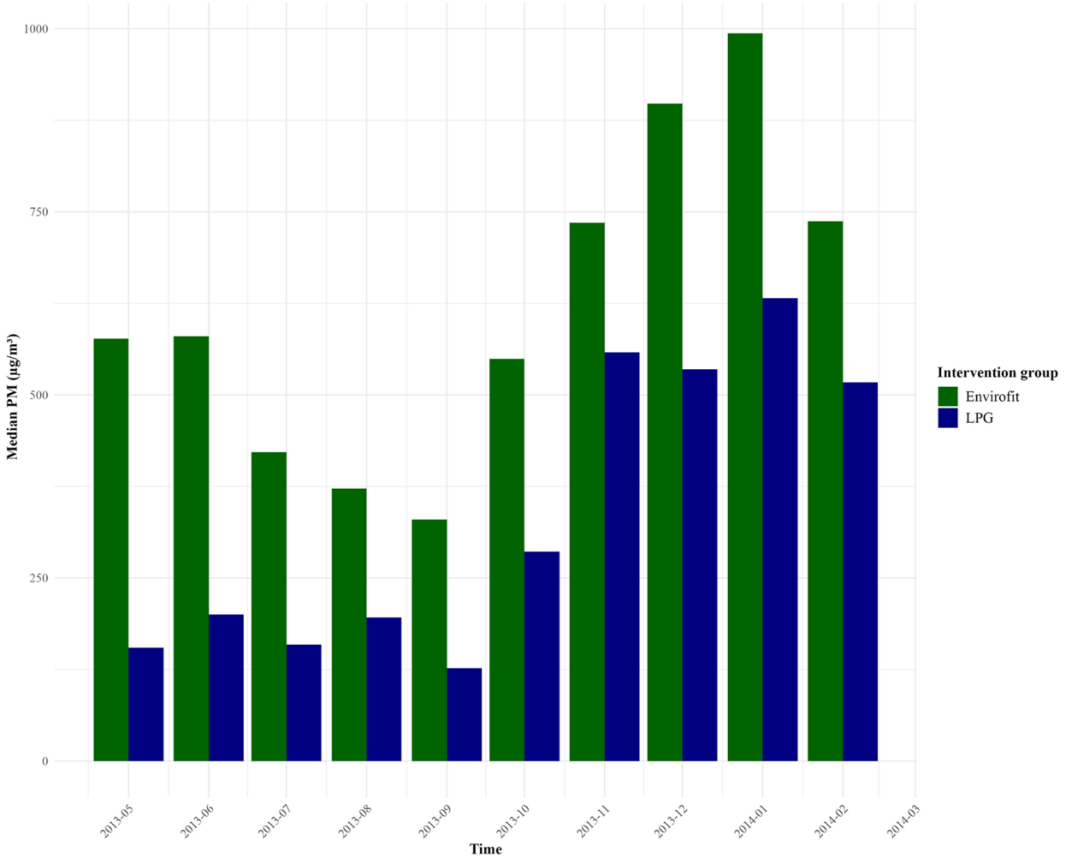
Supplementary Figure 3. Median stove-influenced PM concentration in Trial 1



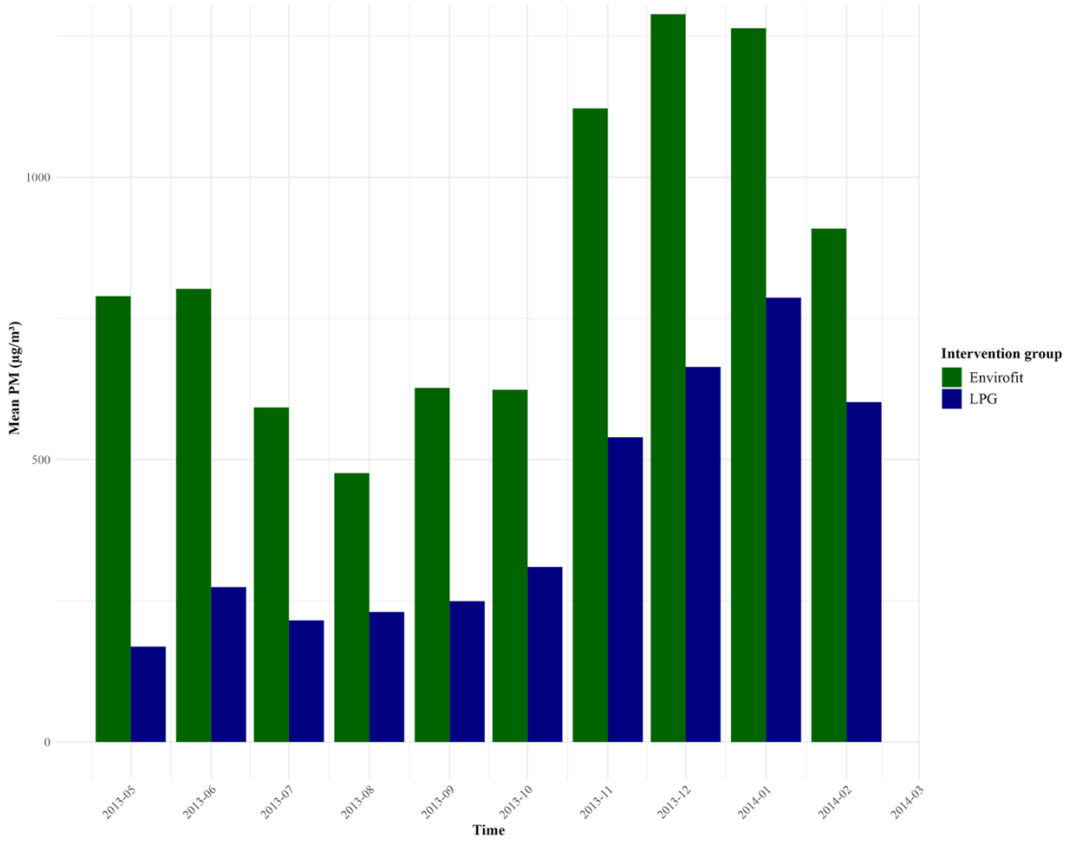
Supplementary Figure 4. Mean stove-influenced PM concentration in Trial 1



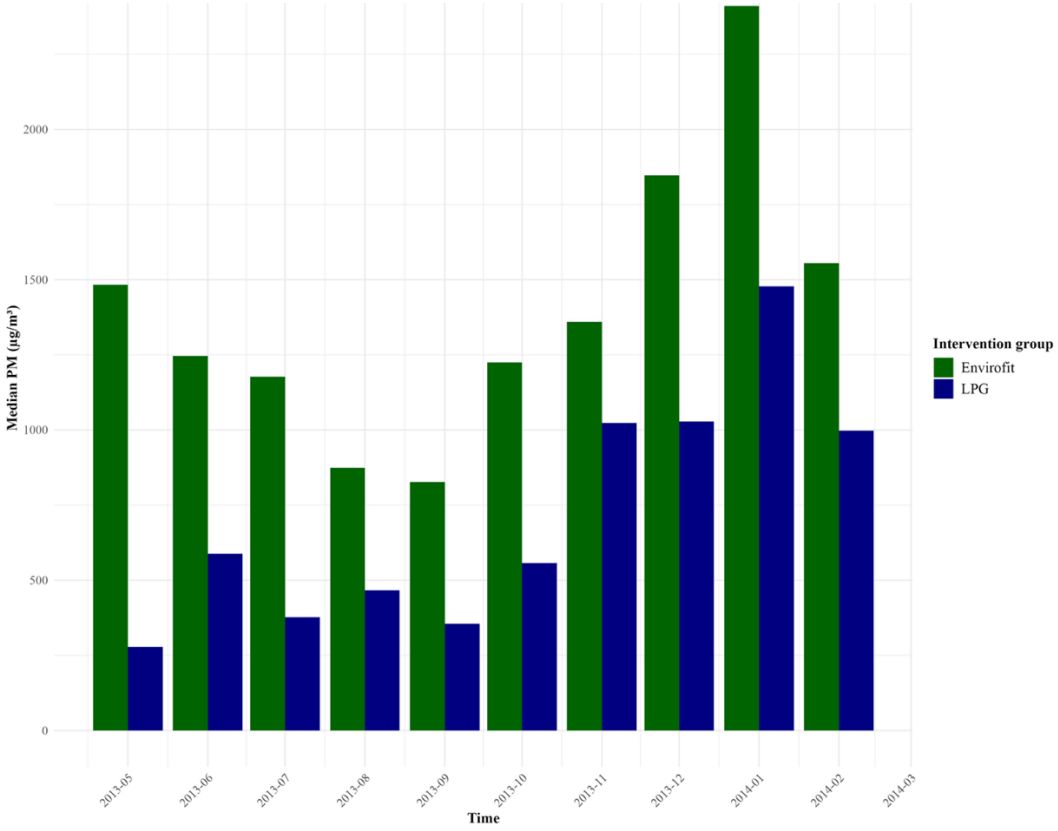
Supplementary Figure 5. Median overall PM concentration in Trial 2



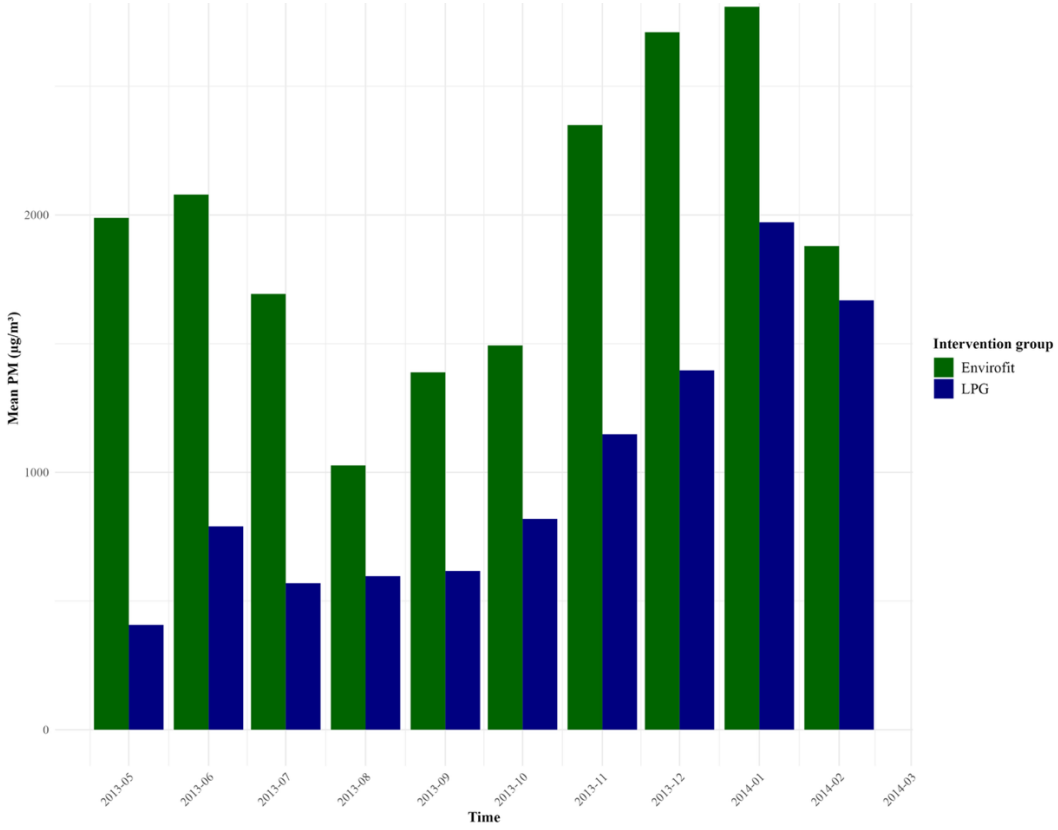
Supplementary Figure 6. Mean overall PM concentration in Trial 2



Supplementary Figure 7. Median stove-influenced l PM concentration in Trial 2



Supplementary Figure 8. Mean stove-influenced PM concentration in Trial 2



Supplementary Table 1. Respiratory morbidity incidence rates in person-year by intervention status in Trial 1 and Trial 2[1-3]

	Trial 1 N = 4,748					
	Pre-intervention			**Post-intervention**		
	ALRI	**ARI**	**ILI**	**ALRI**	**ARI**	**ILI**
N at risk	3,650	3,650	3,650	3,525	3,525	3,525
Total PY	2702.68	2702.68	2702.68	2,932.21	2,932.21	2,932.21
N of cases	933	882	698	263	280	224
Incidence (95% CI)	0.35 (0.32, 0.37)	0.33 (0.31, 0.35)	0.26 (0.24, 0.28)	0.09 (0.08, 0.1)	0.1 (0.09, 0.11)	0.08 (0.07, 0.09)
	Trial 2 N = 2,868					
	Envirofit			**LPG**		
	ALRI	**ARI**	**ILI**	**ALRI**	**ARI**	**ILI**
N at risk	1,404	1,404	1,404	1,464	1,464	1,464
Total PY	1171.59	1171.59	1171.59	1220.73	1220.73	1220.73
N of cases	34	32	26	26	28	26
Incidence (95% CI)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.02 (0.02, 0.03)	0.02 (0.01, 0.03)

1. Number of participants
2. Incidence rate in person-year with 95% confidence intervals
3. ALRI: Acute Lower Respiratory Tract Infection, ARI: Acute Respiratory Tract Infection, ILI: Influenza-like Illness, PY: Person-year, N: Number

Supplementary Table 2. Total and stove-influenced median PM concentrations by intervention status in Trial 1 and Trial 2[1-2]

PM type (ug/m^3)	Trial 1			
	Pre-intervention N = 2,328		Post-intervention N = 2,219	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
Overall				
Total PM	1,123 (1,217)	1416.65 (1175.68)	676 (829.25)	979.64 (1138.88)
Stove-influenced PM	2719 (3149)	3384.44 (2836.46)	1,601 (2100)	2320.44 (2619.75)
Indoor stove				
Total PM	1122 (1219)	1410.16 (1161.59)	692 (847)	981.26 (1152.47)
Stove-influenced PM	2698 (3130)	3371.88 (2830.21)	1596 (2072)	2322.24 (2651.22)
Outdoor stove				
Total PM	1136 (1223)	1512.54 (1363.38)	697 (745)	958.31 (893.44)
Stove-influenced PM	2784 (3332)	3569 (2920.55)	1713 (2359)	2301.17 (2044.58)
PM type (ug/m^3)	**Trial 2**			
	Envirofit N = 638		LPG N = 644	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
Overall				
Total PM	649 (867)	905.33 (950.33)	286 (470)	460.48 (529.27)
Stove-influenced PM	1,347 (1,998)	2045.78 (2202.37)	671 (1,008)	1117.26 (1273.22)
Indoor stove				
Total PM	649 (816)	865.43 (826.9)	284 (459)	460.86 (537.26)
Stove-influenced PM	1,307 (1,918)	1953.61 (2027.85)	670 (1,017)	1124.84 (1017)
Outdoor stove				
Total PM	662 (937)	1070.95 (1334.03)	314 (542)	454.86 (391.59)
Stove-influenced PM	1,360 (2,103)	2427.95 (2103)	694 (921)	1002.09 (921)

1. N = Number of households
2. All comparisons were statistically significant ($p < 0.01$), with p-values calculated using the Wilcoxon rank-sum test

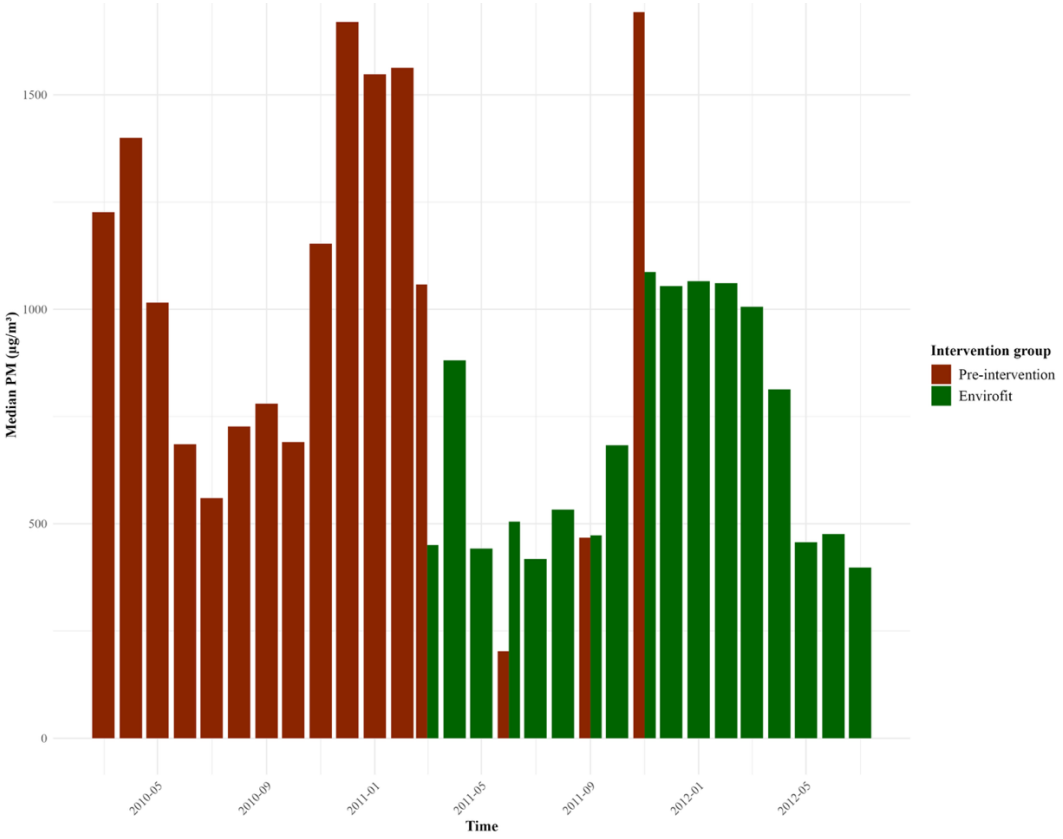
Supplementary Table 3. Stove compliance rate in Trial 1 and Trial 2[1]

Compliance rate (%) Median (IQR)	Trial 1	Trial 2		
	Envirofit N = 2,687	Envirofit N = 902	LPG N = 944	p-value
Use of interventional stove	43.06 (37.38)	61.4 (49.78)	96.15 (7.92)	< 0.001
Use of non-interventional stove	94.55 (15.22)	94.55 (19.67)	11.32 (14.01)	< 0.001

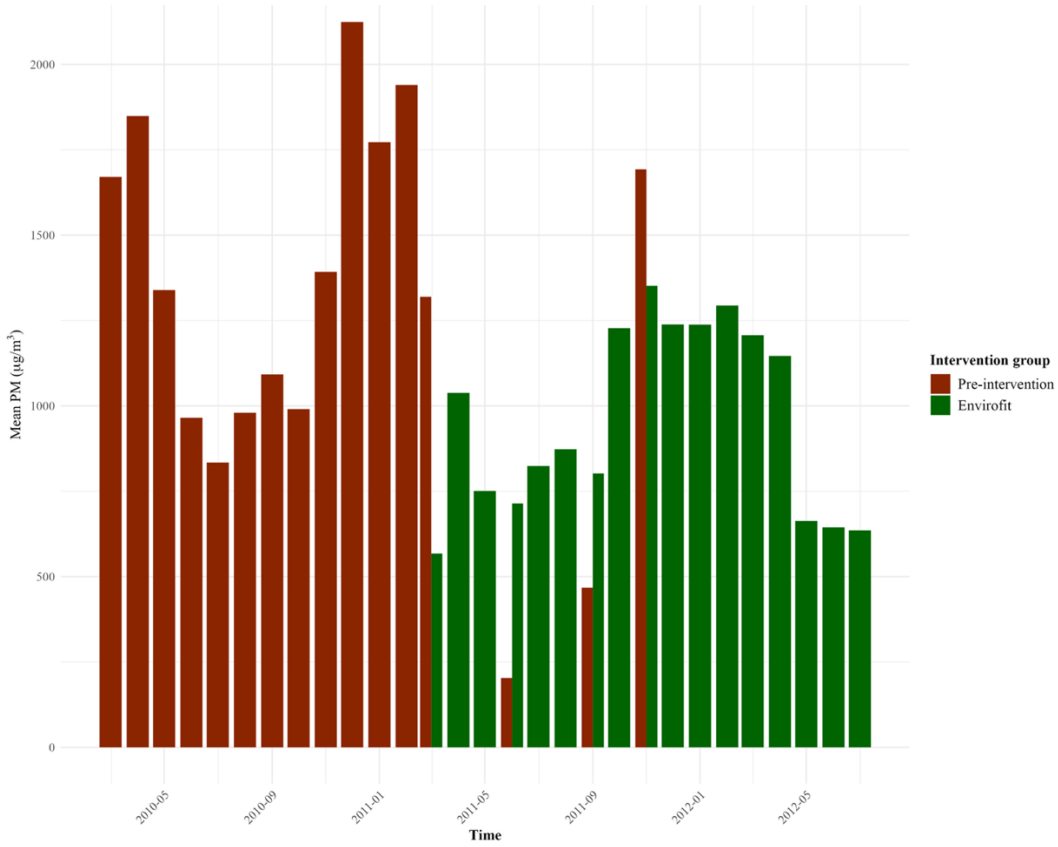
1. N = Number of households, p-value calculated using Wilcoxon-rank sum test comparing compliance rates between Envirofit and LPG groups

Appendix B. Chapter 2 Supplementary Figures and Tables

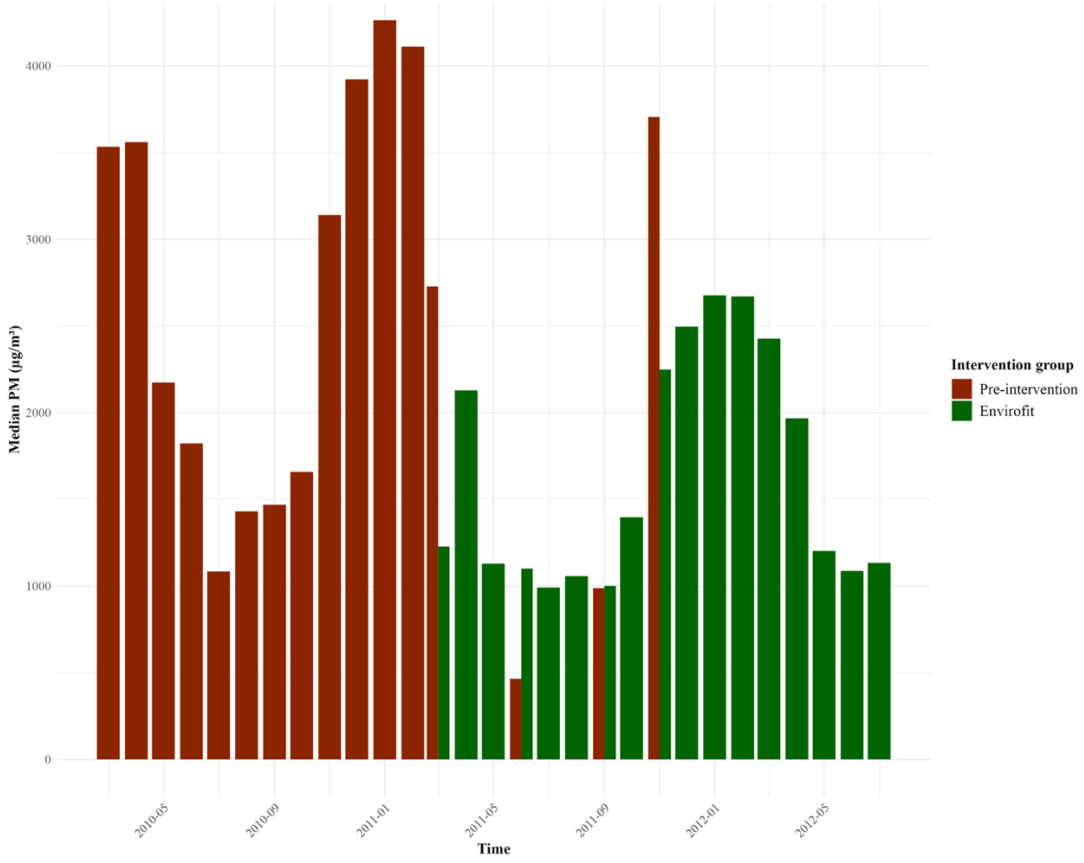
Supplementary Figure 9. Median overall PM concentration in Trial 1



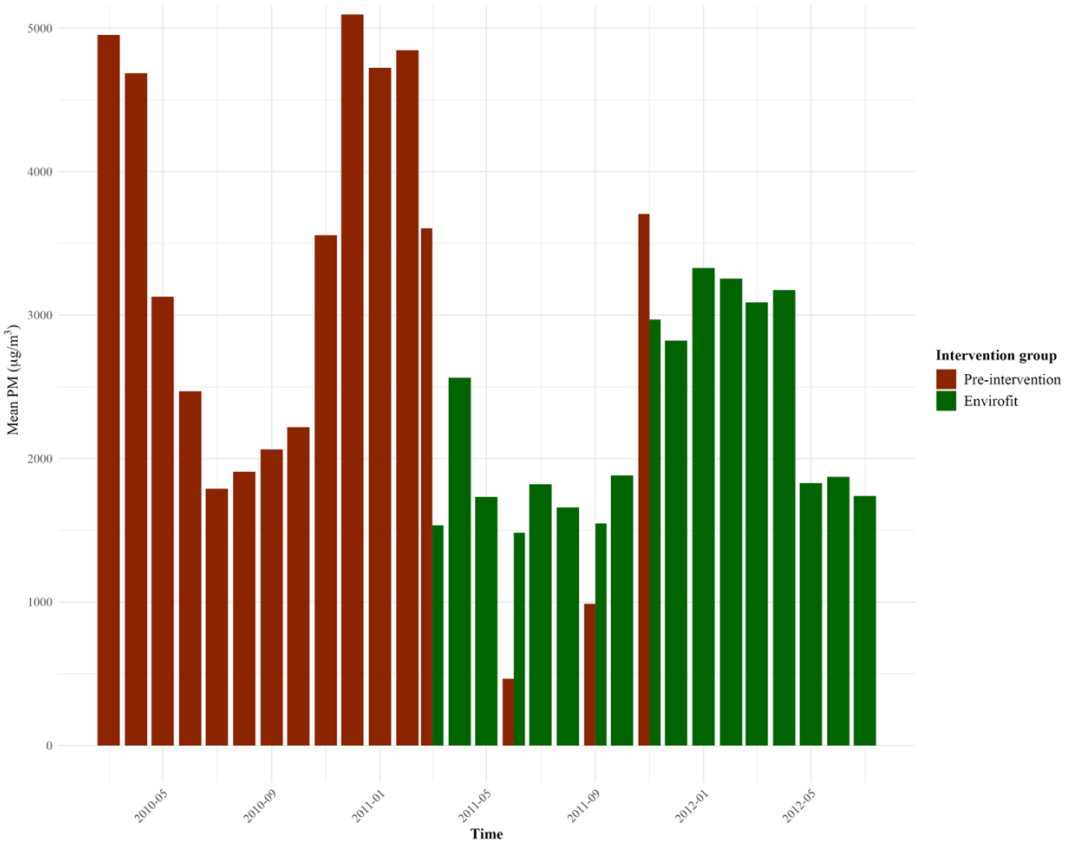
Supplementary Figure 10. Mean overall PM concentration in Trial 1



Supplementary Figure 11. Median stove-influenced PM concentration in Trial 1



Supplementary Figure 12. Mean stove-influenced PM concentration in Trial 1



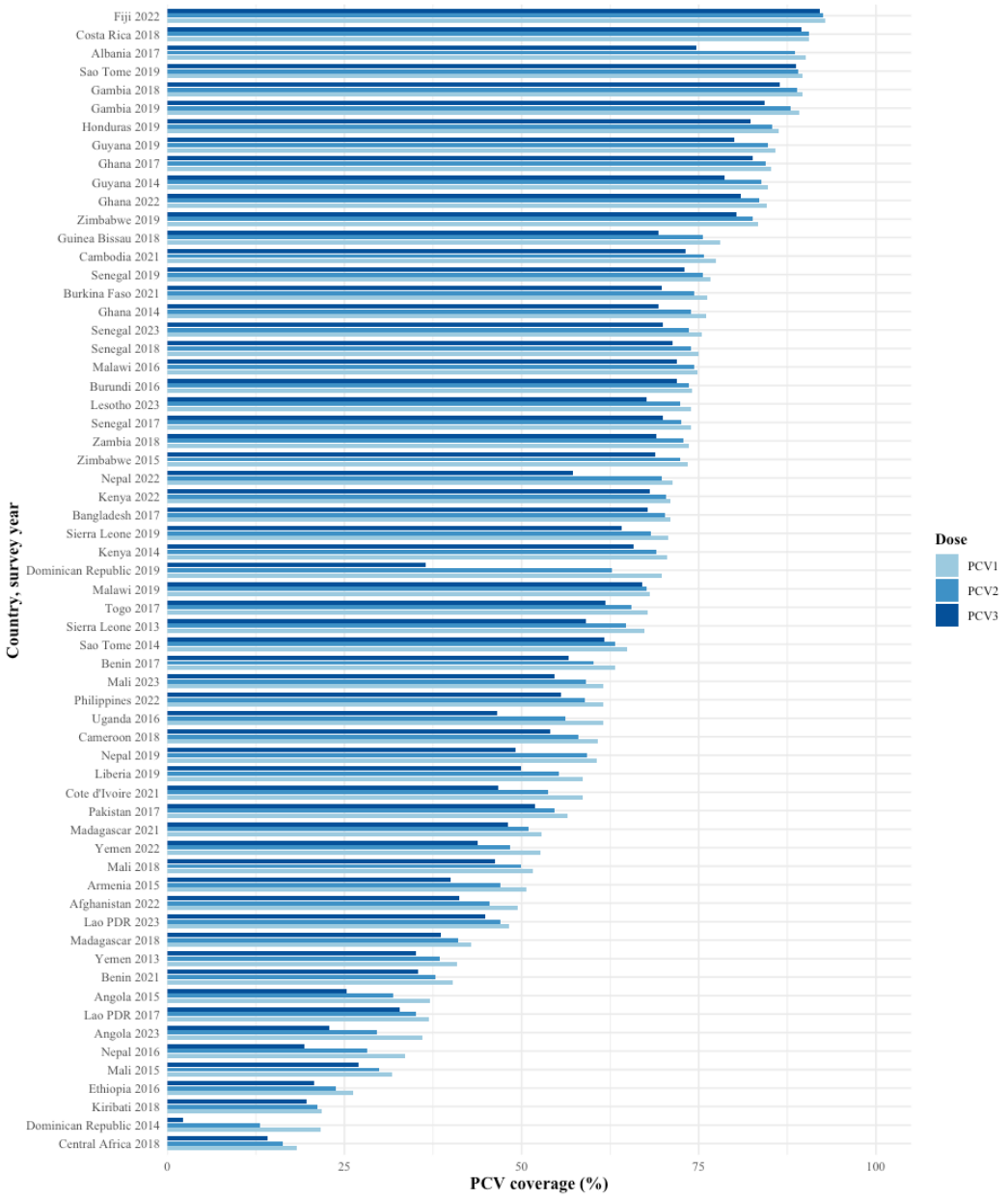
Supplementary Table 4. FEV_1/FEV_6 Pre- and Post-intervention periods[1]

	Pre-intervention		Post-intervention		
	N (%)	**Mean (SD)**	**N (%)**	**Mean (SD)**	**p-value[2]**
Overall	381 (7.24%)	0.859 (0.086)	312 (7.19%)	0.861 (0.084)	0.132
Smoker in household					
Yes	182 (10.27%)	0.846 (0.088)	166 (5.79%)	0.849 (0.089)	0.174
No	199 (5.69%)	0.865 (0.084)	146 (9.93%)	0.867 (0.08)	0.428
SES					
Poor	130 (8.13%)	0.854 (0.087)	104 (7.81%)	0.856 (0.086)	0.467
Middle	134 (7.96%)	0.858 (0.087)	107 (7.84%)	0.861 (0.083)	0.432
Higher	117 (5.91%)	0.863 (0.083)	101 (6.16%)	0.865 (0.082)	0.259
Obese[3]					
Yes	164 (9.83%)	0.856 (0.098)	133 (9.24%)	0.858 (0.093)	0.859
No	213 (6.08%)	0.859 (0.079)	179 (6.2%)	0.862 (0.079)	0.051
Season[4]					
Summer	103 (7.48%)	0.858 (0.086)	103 (8.69%)	0.85 (0.087)	0.003
Monsoon	91 (6.1%)	0.862 (0.08)	87 (7.47%)	0.863 (0.084)	0.235
Autumn	47 (8.27%)	0.852 (0.088)	28 (6.09%)	0.857 (0.076)	0.792
Winter	140 (7.67%)	0.857 (0.089)	94 (6.16%)	0.869 (0.082)	< 0.001
Cookstove location					
Indoor	351 (7.13%)	0.859 (0.085)	294 (7.22%)	0.861 (0.084)	0.239
Outdoor	30 (9.04%)	0.854 (0.095)	17 (6.49%)	0.868 (0.084)	0.1
Chimney installed					
Yes	374 (7.2%)	0.859 (0.086)	304 (7.1%)	0.861 (0.083)	0.994
No	7 (10.61%)	0.85 (0.088)	7 (12.73%)	0.845 (0.099)	0.126

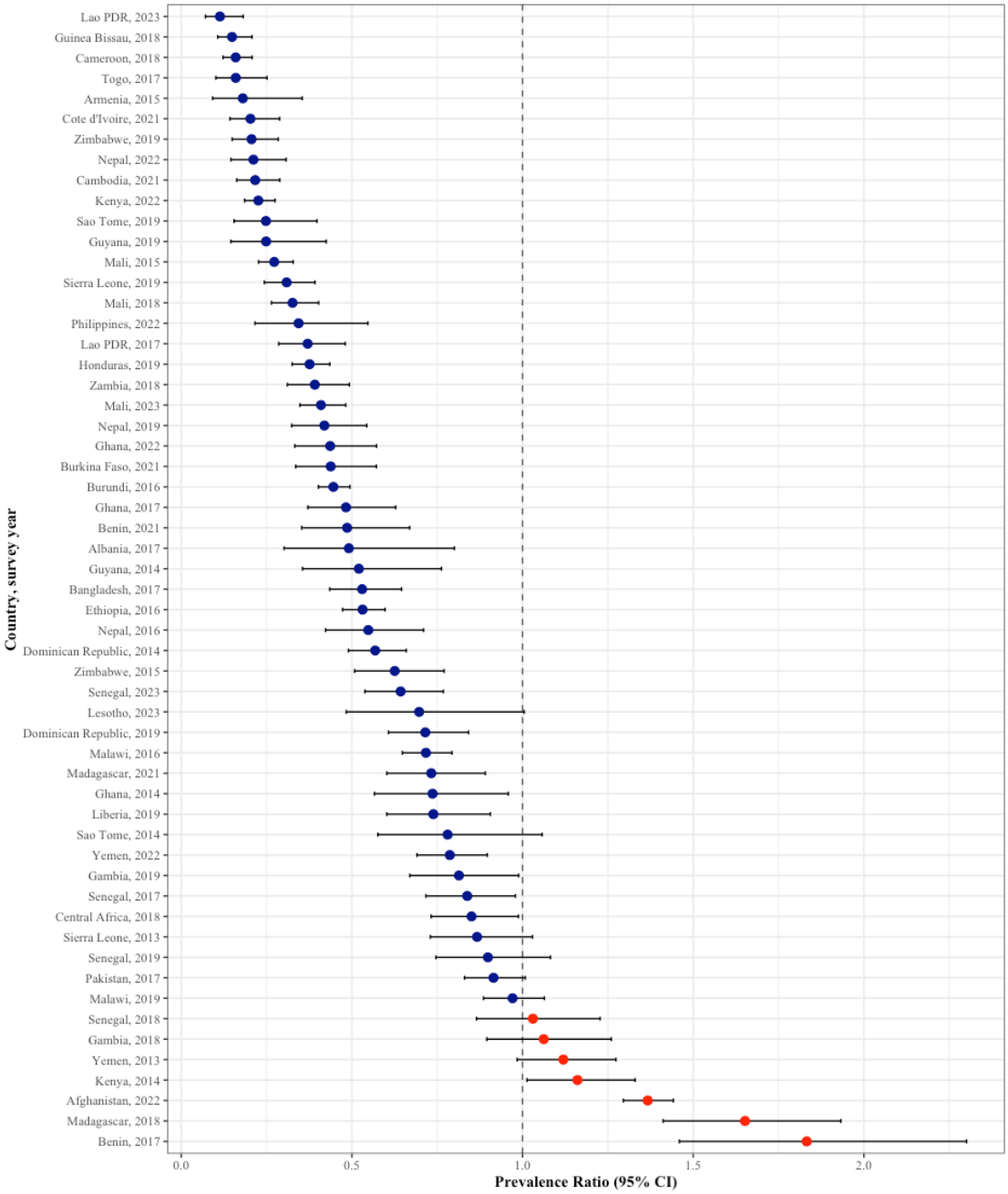
1. SD: Standard Deviation, SES: Socioeconomic Status
2. p-value calculated using Wilcoxon rank-sum test
3. Obesity was defined as having a body mass index (BMI) greater than 27.5
4. Summer runs from March to May, Monsoon runs from June to September, Autumn runs from October to November, and Winter runs from December to February

Appendix C. Chapter 3 Supplementary Figures and Tables

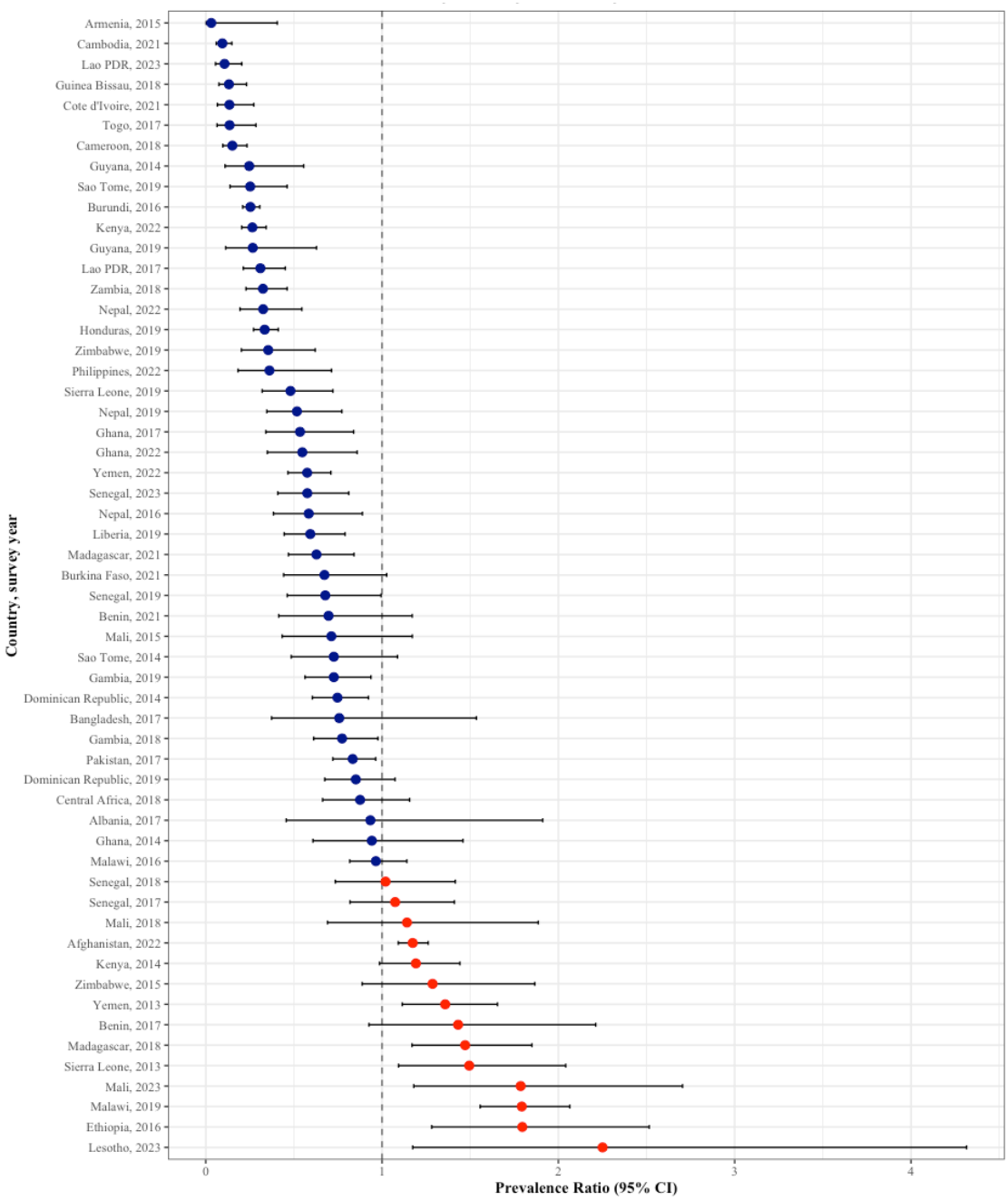
Supplementary Figure 13. PCV Coverage by Country and Survey Year



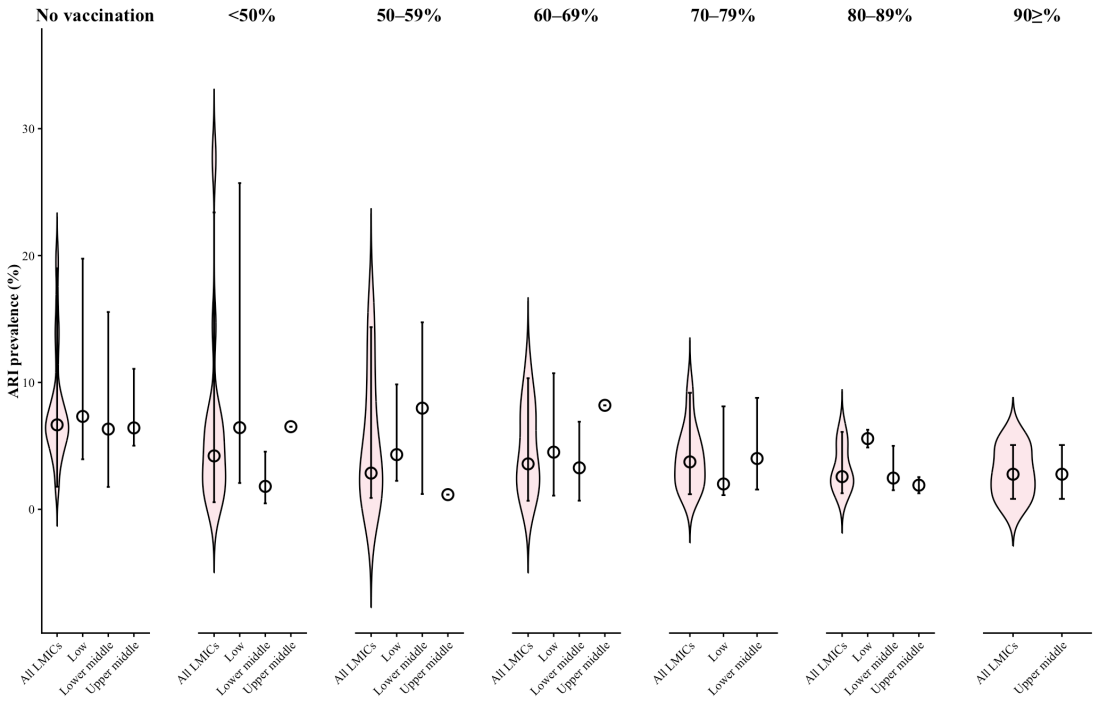
Supplementary Figure 14. ARI Prevalence Ratio by Country and Survey year



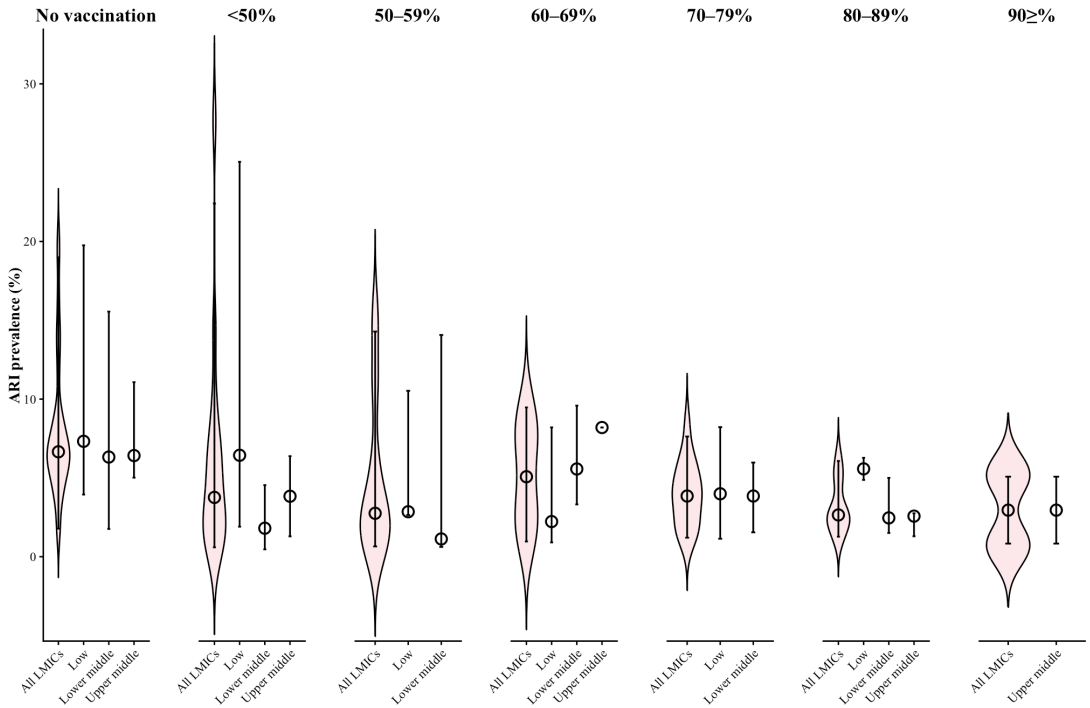
Supplementary Figure 15. Antibiotic use Prevalence Ratio by Country and Survey Year



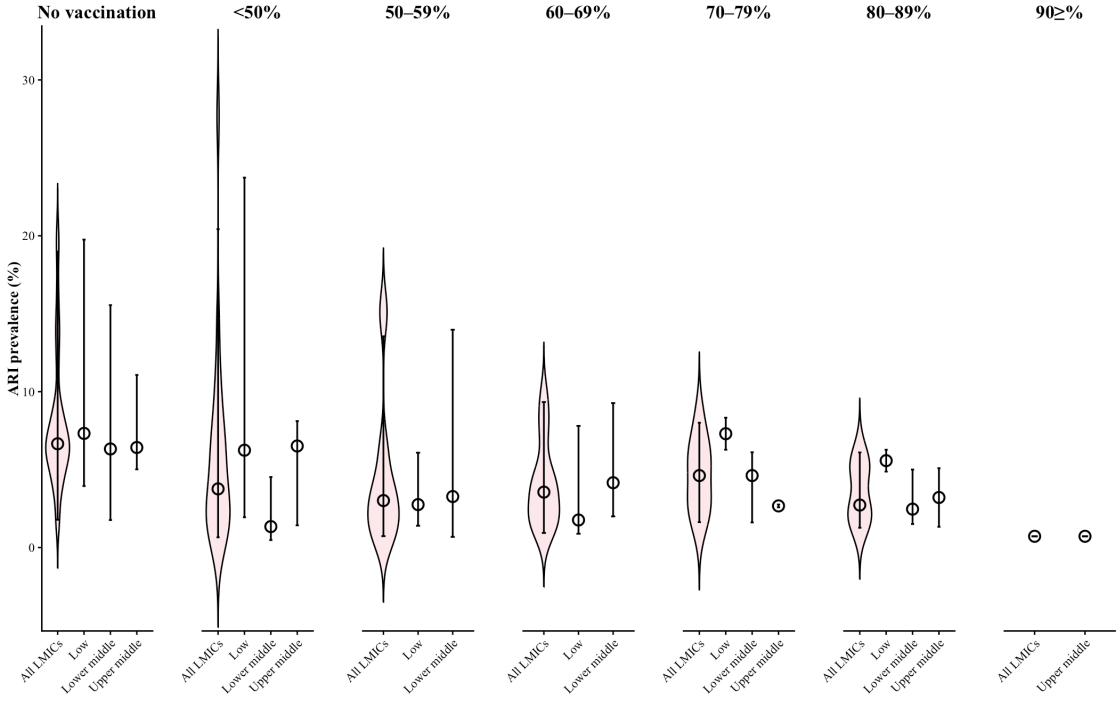
Supplementary Figure 16. PCV1 coverage range by income categories



Supplementary Figure 17. PCV2 coverage range by income categories



Supplementary Figure 18. PCV3 coverage range by income categories



Supplementary Table 5. ARI and Antibiotic use prevalence ratio by country-year[1,2]

Country	Year	PCV status	Total N	ARI N (%)	Abx use N (%)	ARI PR (95% CI)	p-val	Abx use PR (95% CI)	p-val
Afghanistan	2010	Pre	6,758	1,370 (20.27%)	872 (12.90%)	1.3 (1.3, 1.44)	<0.001	1.17 (1.09, 1.26)	<0.001
	2022	Post	15,804	4,377 (27.69%)	2,393 (15.14%)				
Albania	2005	Pre	483	27 (5.63%)	10 (2.13%)	0.49 (0.3, 0.8)	<0.05	0.93 (0.46, 1.91)	0.85
	2017	Post	1,283	35 (2.77%)	26 (1.99%)				
Angola[3]	2015	Post	6,420	242 (3.76%)	129 (2.00%)	-	-	-	-
	2023	Post	4,781	109 (2.27%)	55 (1.15%)				
Armenia	2010	Pre	776	50 (6.42%)	18 (2.26%)	0.19 (0.1, 0.36)	<0.001	0.06 (0.01, 0.38)	<0.05
	2015	Post	854	10 (1.16%)	1 (0.07%)				
Bangladesh	2014	Pre	4,053	267 (6.58%)	17 (0.43%)	0.53 (0.44, 0.65)	<0.001	0.76 (0.37, 1.54)	0.44
	2017	Post	4,189	146 (3.49%)	14 (0.33%)				
Benin	2011	Pre	6,204	111 (1.79%)	34 (0.54%)	1.83 (1.46, 2.3)	<0.001	1.42 (0.92, 2.2)	0.11
	2017	Post	6,397	209 (3.27%)	50 (0.78%)				
	2021	Post	6,433	56 (0.87%)	24 (0.38%)	0.49 (0.36, 0.67)	<0.001	0.7 (0.42, 1.17)	0.18
Burkina Faso	2006	Pre	2,894	56 (0.87%)	24 (0.38%)	0.44 (0.34, 0.57)	<0.001	0.67 (0.44, 1.03)	0.07
	2016	Post	5,407	117 (4.03%)	38 (1.33%)				
Burundi	2010	Pre	3,862	96 (1.77%)	48 (0.89%)	0.45 (0.4, 0.49)	<0.001	0.25 (0.21, 0.31)	<0.001
Burundi	2016	Post	6,543	727 (18.81%)	339 (8.78%)				
Cambodia	2014	Pre	3,589	549 (8.38%)	146 (2.23%)	0.22 (0.16, 0.29)	<0.001	0.1 (0.06, 0.15)	<0.001
Cambodia	2021	Post	3,960	236 (6.59%)	196 (5.47%)				
Cameroon	2006	Pre	3,264	57 (1.43%)	20 (0.51%)	0.16 (0.12, 0.21)	<0.001	0.15 (0.1, 0.23)	<0.001
Cameroon	2018	Post	4,675	287 (8.80%)	111 (3.40%)				
Central Africa	2010	Pre	5,439	66 (1.40%)	24 (0.51%)	0.85 (0.73, 0.99)	<0.05	0.88 (0.66, 1.16)	0.35
	2018	Post	4,254	266 (6.24%)	82 (1.92%)				
Costa Rica[3]	2018	Post	187,870	9,751 (5.19%)	4,342 (2.31%)	-	-	-	-
Cote d'Ivoire	2011	Pre	3,569	150 (4.20%)	53 (1.48%)	0.2 (0.14, 0.29)	<0.001	0.13 (0.07, 0.27)	<0.001
	2021	Post	4,497	38 (0.85%)	9 (0.20%)				
Dominican Republic	2013	Pre	1,783	204 (11.46%)	101 (5.64%)	0.57 (0.49, 0.66)	<0.001	0.74 (0.6, 0.92)	<0.05
	2014	Post	10,182	663 (6.51%)	429 (4.21%)				

	2019	Post	4,290	352 (8.20%)	206 (4.80%)	0.71 (0.61, 0.84)	<0.001	0.85 (0.67, 1.07)	0.17
Ethiopia	2005	Pre	4,840	711 (14.70%)	51 (1.06%)	0.53 (0.47, 0.6)	<0.001	1.8 (1.28, 2.52)	<0.001
	2016	Post	5,019	392 (7.81%)	95 (1.90%)				
Fiji[3]	2022	Post	1,074	8 (0.72%)	5 (0.49%)	-	-	-	-
Gambia	2005	Pre	3,550	211 (5.94%)	134 (3.79%)	1.06 (0.89, 1.26)	0.49	0.77 (0.61, 0.98)	<0.05
	2018	Post	4,727	298 (6.31%)	138 (2.93%)				
	2019	Post	3,638	176 (4.84%)	100 (2.75%)	0.81 (0.67, 0.99)	<0.05	0.73 (0.56, 0.94)	<0.05
Ghana	2006	Pre	1,705	96 (5.65%)	32 (1.90%)	0.74 (0.57, 0.96)	<0.05	0.94 (0.61, 1.45)	0.77
	2014	Post	2,796	116 (4.16%)	50 (1.79%)				
	2017	Post	4,319	118 (2.73%)	44 (1.02%)	0.48 (0.37, 0.63)	<0.001	0.53 (0.34, 0.83)	<0.05
	2022	Post	4,237	104 (2.46%)	44 (1.04%)	0.44 (0.33, 0.57)	<0.001	0.55 (0.35, 0.85)	<0.05
Guinea Bissau	2012	Pre	3,199	234 (7.32%)	91 (2.84%)	0.15 (0.11, 0.21)	<0.001	0.13 (0.07, 0.23)	<0.001
	2018	Post	3,690	40 (1.09%)	14 (0.37%)				
Guyana	2006	Pre	1,229	61 (4.95%)	23 (1.85%)	0.52 (0.36, 0.76)	<0.001	0.26 (0.12, 0.57)	<0.001
	2014	Post	1,696	44 (2.58%)	8 (0.46%)				
	2019	Post	1,360	17 (1.23%)	7 (0.49%)	0.25 (0.15, 0.43)	<0.001	0.28 (0.12, 0.64)	<0.05
Honduras	2005	Pre	5,160	721 (13.97%)	404 (7.83%)	0.38 (0.32, 0.44)	<0.001	0.34 (0.27, 0.41)	<0.001
	2019	Post	4,112	216 (5.26%)	108 (2.62%)				
Kenya	2008	Pre	2,835	239 (8.42%)	127 (4.48%)	1.16 (1.01, 1.33)	<0.05	1.19 (0.98, 1.44)	0.07
	2014	Post	9,446	923 (9.78%)	504 (5.34%)				
	2022	Post	8,392	160 (1.90%)	99 (1.18%)	0.23 (0.19, 0.27)	<0.001	0.26 (0.2, 0.34)	<0.001
Kiribati[3]	2018	Post	1,097	51 (4.66%)	37 (3.33%)	-	-	-	-
Lao PDR	2012	Pre	5,459	198 (3.63%)	110 (2.01%)	0.37 (0.3, 0.46)	<0.001	0.31 (0.22, 0.45)	<0.001
	2017	Post	1,723	77 (1.34%)	36 (0.62%)				
	2023	Post	1,145	19 (0.41%)	10 (0.21%)	0.12 (0.07, 0.18)	<0.001	0.11 (0.06, 0.21)	<0.001
Lesotho	2014	Pre	1,569	82 (5.20%)	14 (0.92%)	0.7	0.05	2.22	<0.05

	2023	Post	1,145	42 (3.63%)	24 (2.06%)	(0.48, 1.00)		(1.17, 4.22)	
Liberia	2013	Pre	3,086	241 (7.80%)	145 (4.71%)	0.74 (0.6, 0.91)	<0.05	0.6 (0.45, 0.79)	<0.001
	2019	Post	2,338	135 (5.76%)	65 (2.79%)				
Madagascar	2008	Pre	5,968	233 (3.90%)	117 (1.96%)	1.65 (1.41, 1.93)	<0.001	1.47 (1.17, 1.85)	<0.001
	2018	Post	6,362	409 (6.44%)	183 (2.88%)				
	2021	Post	5,821	166 (2.85%)	72 (1.23%)	0.73 (0.6, 0.89)	<0.05	0.63 (0.47, 0.84)	<0.05
Malawi	2006	Pre	12,780	1,109 (8.68%)	351 (2.75%)	0.72 (0.65, 0.79)	<0.001	0.97 (0.82, 1.14)	0.68
	2016	Post	8,183	509 (6.22%)	217 (2.65%)				
	2019	Post	7,968	671 (8.42%)	392 (4.92%)	0.97 (0.89, 1.06)	0.53	1.79 (1.56, 2.06)	<0.001
Mali	2006	Pre	6,354	428 (6.73%)	33 (0.52%)	0.27 (0.23, 0.33)	<0.001	0.71 (0.44, 1.17)	0.18
	2015	Post	7,291	145 (1.83%)	29 (0.37%)				
	2018	Post	4,758	104 (2.20%)	28 (0.59%)	0.33 (0.27, 0.4)	<0.001	1.14 (0.7, 1.88)	0.6
	2023	Post	7,400	204 (2.75%)	68 (0.92%)	0.41 (0.35, 0.48)	<0.001	1.77 (1.17, 2.68)	<0.05
Nepal	2011	Pre	2,504	157 (6.26%)	59 (2.36%)	0.55 (0.42, 0.71)	<0.001	0.59 (0.39, 0.89)	<0.05
	2016	Post	2,452	84 (3.43%)	34 (1.38%)				
	2019	Post	3,214	84 (2.63%)	39 (1.22%)	0.42 (0.32, 0.54)	<0.001	0.52 (0.35, 0.77)	<0.05
	2022	Post	2,459	33 (1.32%)	19 (0.77%)	0.21 (0.15, 0.31)	<0.001	0.33 (0.2, 0.55)	<0.001
Pakistan	2006	Pre	4,010	662 (16.50%)	340 (8.47%)	0.91 (0.83, 1.01)	0.07	0.83 (0.72, 0.96)	<0.05
	2017	Post	4,710	711 (15.09%)	333 (7.06%)				
Philippines	2017	Pre	4,753	83 (1.75%)	37 (0.79%)	0.35 (0.22, 0.55)	<0.001	0.37 (0.19, 0.73)	<0.05
	2022	Post	3,730	22 (0.60%)	11 (0.29%)				
Sao Tome	2008	Pre	886	82 (9.28%)	50 (5.66%)	0.78 (0.58, 1.06)	0.11	0.73 (0.49, 1.09)	0.12
	2014	Post	988	72 (7.24%)	41 (4.11%)	0.25 (0.16, 0.4)	<0.001	0.26 (0.14, 0.47)	<0.001
	2019		906	21 (2.30%)	13 (1.43%)	0.84 (0.72, 0.98)	<0.05	1.07 (0.82, 1.41)	0.61

Senegal	2010	Pre	5,492	329 (5.99%)	99 (1.79%)	1.03 (0.87, 1.23)	0.73	1.02 (0.74, 1.42)	0.89
	2017	Post	5,467	274 (5.02%)	105 (1.93%)				
	2018	Post	2,984	184 (6.17%)	55 (1.83%)				
	2019	Post	2,876	155 (5.38%)	35 (1.22%)	0.9 (0.75, 1.08)	0.26	0.68 (0.47, 1.00)	0.05
	2023	Post	4,650	179 (3.85%)	48 (1.03%)	0.64 (0.54, 0.77)	<0.001	0.58 (0.41, 0.81)	<0.05
Sierra Leone	2008	Pre	2,634	190 (7.22%)	51 (1.95%)	0.87 (0.73, 1.03)	0.1	1.48 (1.09, 2.03)	<0.05
	2013	Post	5,335	334 (6.26%)	155 (2.91%)				
	2019	Post	4,449	99 (2.23%)	42 (0.94%)	0.31 (0.24, 0.39)	<0.001	0.48 (0.32, 0.72)	<0.001
Togo	2010	Pre	2,357	127 (5.39%)	55 (2.33%)	0.16 (0.1, 0.25)	<0.001	0.14 (0.06, 0.28)	<0.001
	2017	Post	2,491	21 (0.86%)	8 (0.32%)				
Uganda[3]	2016	Post	7,330	810 (11.06%)	361 (4.92%)	-	-	-	-
Yemen	2006	Pre	1,894	245 (12.94%)	109 (5.77%)	1.12 (0.98, 1.27)	0.09	1.35 (1.11, 1.65)	<0.001
	2013	Post	7,643	1,107 (14.48%)	599 (7.84%)				
	2022	Post	10,108	1,029 (10.18%)	335 (3.32%)	0.79 (0.69, 0.9)	<0.001	0.57 (0.47, 0.71)	<0.001
Zambia	2007	Pre	3,071	186 (6.07%)	92 (3.00%)	0.39 (0.31, 0.49)	<0.001	0.33 (0.23, 0.46)	<0.001
	2018	Post	4,677	111 (2.38%)	46 (0.97%)				
Zimbabwe	2009	Pre	3,547	244 (6.88%)	53 (1.48%)	0.63 (0.51, 0.77)	<0.001	1.29 (0.89, 1.86)	0.18
	2015	Post	2,979	128 (4.30%)	57 (1.91%)				
	2019	Post	3,001	43 (1.42%)	16 (0.53%)	0.21 (0.15, 0.29)	<0.001	0.36 (0.21, 0.63)	<0.001

1. For countries with more than one post-PCV survey, each pre-PCV survey was used for the prevalence ratio calculation
2. PCV: Pneumococcal conjugate vaccine, ARI: Acute respiratory infection, Abx: Antibiotic, PR: Prevalence ratio, p-val: p-value
3. No pre-PCV surveys

Supplementary Table 6. Annual mean PCV coverage overall and by country income group

Year	Total country	Income group	Total children	PCV1		PCV2		PCV3	
				N[1]	Mean Coverage (%)	N[1]	Mean Coverage (%)	N[1]	Mean Coverage (%)
2013	2	Overall	12,977	6,714	54.09%	6,389	51.57%	5,834	47.08%
	2	Low	12,977	6,714	54.09%	6,389	51.57%	5,834	47.08%
	-	Lower-middle	-	-	-	-	-	-	-
	-	Upper-middle	-	-	-	-	-	-	-
2014	5	Overall	25,107	13,077	63.61%	11,955	60.58%	10,312	
	-	Low	-	-		-		-	
	3	Lower-middle	13,230	9,438	70.55%	9,206	68.68%	8,758	65.58%
	2	Upper-middle	11,877	3,638	53.21%	2,749	48.43%	1,554	40.40%
2015	4	Overall	18,174	7,513	48.23%	6,973	45.28%	6,161	40.30%
	1	Low	7,921	2,512	31.72%	2,370	29.92%	2,141	27.03%
	2	Lower-middle	9,399	4,568	55.28%	4,202	52.13%	3,679	47.12%
	1	Upper-middle	854	432	50.65%	401	46.94%	341	39.95%
2016	5	Overall	29,528	17,622	54.06%	16,904	51.23%	15,518	46.08%
	4	Low	27,076	16,798	59.17%	16,212	56.98%	15,044	52.77%
	1	Lower-middle	2,452	824	33.62%	692	28.22%	474	19.32%
	-	Upper-middle	-	-	-	-	-	-	-
2017	8	Overall	34,623	22,364	68.07%	21,764	66.40%	20,696	62.29%
	1	Low	2,491	1,691	67.87%	1,633	65.55%	1,540	61.81%
	6	Lower-middle	30,849	19,517	64.42%	18,993	62.83%	18,198	60.31%
	1	Upper-middle	1,283	1,157	90.18%	1,137	88.65%	958	74.65%
2018	11	Overall	225,093	192,106	60.22%	191,303	58.82%	188,167	55.82%
	5	Low	23,790	13,071	56.07%	12,667	54.33%	11,894	50.92%
	5	Lower-middle	13,433	8,766	57.81%	8,559	56.51%	8,100	53.53%
	1	Upper-middle	187,870	170,268	90.63%	170,077	90.53%	168,173	89.52%
2019	11	Overall	38,153	28,368	76.26%	27,641	74.41%	25,356	68.67%
	4	Low	18,394	13,196	71.71%	12,924	69.79%	12,425	66.32%

	5	Lower-middle	14,109	11,014	79.31%	10,869	78.34%	10,280	74.72%
	2	Upper-middle	5,650	4,158	77.75%	3,848	73.81%	2,651	58.23%
2021	5	Overall	26,118	15,496	61.10%	14,841	58.54%	13,838	54.59%
	2	Low	11,228	7,193	64.50%	6,990	62.69%	6,568	58.90%
	3	Lower-middle	14,890	8,303	58.84%	7,851	55.77%	7,270	51.72%
	-	Upper-middle	-	-	-	-	-	-	-
2022	7	Overall	45,803	27,729	69.07%	26,448	67.01%	24,544	62.69%
	2	Low	25,912	13,142	51.08%	12,094	47.00%	10,940	42.51%
	4	Lower-middle	18,818	13,589	72.10%	13,361	70.65%	12,614	65.42%
	1	Upper-middle	1,074	998	92.92%	993	92.51%	989	92.15%
2023	5	Overall	22,567	12,847	59.04%	12,198	56.35%	11,225	51.99%
	1	Low	7,400	4,556	61.57%	4,374	59.11%	4,045	54.67%
	4	Lower-middle	15,167	8,290	58.41%	7,824	55.66%	7,179	51.32%
	-	Upper-middle	-	-	-	-	-	-	-

1. Number of children who received each respective PCV dose

Supplementary Table 7. Association Between PCV Introduction and Antibiotic Use During a Diarrheal Episode[1]

Group	Level	Antibiotic use		
		aß (95% CI)	p-val	p-val[2]
Overall	-	0.009 (-0.012, 0.03)	0.361	-
Age	6-11 m	0.013 (-0.014, 0.04)	0.314	0.079
	12-23 m	0.008 (-0.009, 0.026)	0.312	
	24-35 m	0.002 (-0.016, 0.019)	0.842	
Baseline ARI	< 5%	-0.014 (-0.038, 0.01)	0.143	0.499
	5-9%	0.064 (0.02, 0.108)	0.027	
	≥10%	-0.001 (-0.021, 0.02)	0.94	

1. PCV: Pneumococcal conjugate vaccine, m: months
2. p-value calculated by Wald test

Supplementary Table 8. Association Between PCV coverages and Antibiotic Use During a Diarrheal Episode[1]

Group	Dose	Level	aß (95% CI)	p-val	p-val	aRD (95% CI)	p-val	p-val
Overall	PCV1	-	0.008 (-0.019, 0.034)	0.547	-	-0.018 (-0.288, 0.251)	0.832	-
	PCV2	-	0.008 (-0.019, 0.035)	0.562	-	-0.02 (-0.271, 0.23)	0.803	-
	PCV3	-	0.009 (-0.019, 0.037)	0.492	-	-0.012 (-0.282, 0.257)	0.898	-
Age	PCV1	6-11 m	0.01 (-0.021, 0.042)	0.506	0.068	-0.095 (-0.282, 0.092)	0.16	0.397
		12-23 m	0.01 (-0.012, 0.032)	0.352		0.003 (-0.161, 0.167)	0.954	
		24-35 m	-0.006 (-0.024, 0.013)	0.533		0.07 (-0.227, 0.367)	0.552	
	PCV2	6-11 m	-0.089 (-0.255, 0.076)	0.158	0.488	-0.095 (-0.267, 0.078)	0.153	0.371
		12-23 m	0.003 (-0.15, 0.155)	0.951		0.003 (-0.148, 0.154)	0.942	
		24-35 m	0.018 (-0.289, 0.324)	0.892		0.004 (-0.305, 0.314)	0.973	
	PCV3	6-11 m	-0.112 (-0.312, 0.087)	0.169	0.533	-0.116 (-0.329, 0.097)	0.178	0.496
		12-23 m	0.007 (-0.139, 0.153)	0.884		0.008 (-0.137, 0.153)	0.865	
		24-35 m	0.034 (-0.226, 0.295)	0.749		0.014 (-0.282, 0.309)	0.903	
Baseline ARI[3]	PCV1	< 5%	-0.014 (-0.079, 0.051)	0.522	0.491	-	-	-
		5-9%	0.003 (-0.024, 0.03)	0.581		-	-	-
		≥10%	0.057 (-0.571, 0.685)	0.589		-	-	-
	PCV2	< 5%	-0.013 (-0.082, 0.057)	0.564	0.426	-	-	-
		5-9%	0.003 (-0.025, 0.031)	0.696		-	-	-
		≥10%	0.042 (-0.744, 0.827)	0.801		-	-	-
	PCV3	< 5%	-0.013 (-0.086, 0.06)	0.803	0.717	-	-	-
		5-9%	0.002 (-0.026, 0.03)	0.822		-	-	-
		≥10%	0.036 (-0.892, 0.964)	0.878		-	-	-

1. PCV: Pneumococcal conjugate vaccine, RD: Risk difference m: months
2. p-value calculated by Wald test
3. Insufficient heterogeneity in risk differences by baseline ARI prevalence

Supplementary Table 9. Under-five mortality rate 5 years preceding each survey year

Country	Year	PCV status	Total N	Mortality rate (per 1,000 live births)
Afghanistan	2010	Pre	6,758	102
	2022	Post	15,804	55
Albania	2005	Pre	483	19
	2017	Post	1,283	-
Angola	2015	Post	6,420	68
	2023	Post	4,781	52
Armenia	2010	Pre	776	16
	2015	Post	854	0
Bangladesh	2014	Pre	4,053	46
	2017	Post	4,189	45
Benin	2011	Pre	6,204	70
	2017	Post	6,397	96
	2021	Post	6,433	80
Burkina Faso	2006	Pre	2,894	188
	2016	Post	5,407	70
Burundi	2010	Pre	3,862	96
Burundi	2016	Post	6,543	78
Cambodia	2014	Pre	3,589	35
Cambodia	2021	Post	3,960	16
Cameroon	2006	Pre	3,264	144
Cameroon	2018	Post	4,675	28
Central Africa	2010	Pre	5,439	179
	2018	Post	4,254	99
Costa Rica	2018	Post	187,870	-
Cote d'Ivoire	2011	Pre	3,569	43
	2021	Post	4,497	74
Dominican Republic	2013	Pre	1,783	31
	2014	Post	10,182	35
	2019	Post	4,290	32
Ethiopia	2005	Pre	4,840	123
	2016	Post	5,019	67
Fiji	2022	Post	1,074	18
Gambia	2005	Pre	3,550	131
	2018	Post	4,727	57
	2019	Post	3,638	56
Ghana	2006	Pre	1,705	71
	2014	Post	2,796	60
	2017	Post	4,319	56
	2022	Post	4,237	40
Guinea Bissau	2012	Pre	3,199	123
	2018	Post	3,690	51
Guyana	2006	Pre	1,229	47
	2014	Post	1,696	39
	2019	Post	1,360	25

Honduras	2005	Pre	5,160	23
	2019	Post	4,112	21
Kenya	2008	Pre	2,835	74
	2014	Post	9,446	52
	2022	Post	8,392	41
Kiribati	2018	Post	1,097	61
Lao PDR	2012	Pre	5,459	79
	2017	Post	1,723	46
	2023	Post	1,145	28
Lesotho	2014	Pre	1,569	85
	2023	Post	1,145	76
Liberia	2013	Pre	3,086	54
	2019	Post	2,338	94
Madagascar	2008	Pre	5,968	93
	2018	Post	6,362	72
	2021	Post	5,821	590
Malawi	2006	Pre	12,780	75
	2016	Post	8,183	122
	2019	Post	7,968	63
Mali	2006	Pre	6,354	56
	2015	Post	7,291	191
	2018	Post	4,758	108
	2023	Post	7,400	54
Nepal	2011	Pre	2,504	87
	2016	Post	2,452	54
	2019	Post	3,214	39
	2022	Post	2,459	28
Pakistan	2006	Pre	4,010	38
	2017	Post	4,710	94
Philippines	2017	Pre	4,753	74
	2022	Post	3,730	27
Sao Tome	2008	Pre	886	26
	2014	Post	988	63
	2019	Post	906	45
Senegal	2010	Pre	5,492	14
	2017	Post	5,467	72
	2018	Post	2,984	56
	2019	Post	2,876	51
	2023	Post	4,650	37
Sierra Leone	2008	Pre	2,634	40
	2013	Post	5,335	140
	2019	Post	4,449	156
Togo	2010	Pre	2,357	122
	2017	Post	2,491	124
Uganda[3]	2016	Post	7,330	71
Yemen	2006	Pre	1,894	64
	2013	Post	7,643	78
	2022	Post	10,108	53
Zambia	2007	Pre	3,071	6

	2018	Post	4,677	119
Zimbabwe	2009	Pre	3,547	61
	2015	Post	2,979	86
	2019	Post	3,001	69