Antibiotic use and respiratory pathogens with focus on *Streptococcus pneumoniae* in Tanzanian children

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Cover illustration: Central Moshi by night. Photographer: Johan Franzén.

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“For none of us lives for ourselves alone”

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ABSTRACT

This thesis describes the epidemiology of *Streptococcus pneumoniae* (pneumococci) and other respiratory pathogens after introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) and further portrays antibiotic use in Tanzanian children. Pneumococci are a leading cause of pneumonia in children. However, respiratory infections among children may be associated with over-use of antibiotics leading to bacterial resistance, a significant threat to global child health.

In a *quantitative* study, conducted in urban Moshi, Northern Tanzania 2013-2015, 775 children <2 years of age attending public primary healthcare facilities for routine care were sampled from the nasopharynx. Structured interviews with the parent/guardian revealed that more than half of the children had received antibiotics in the past 3 months. Isolated pneumococci (n=244) showed increasing resistance to phenoxymethylpenicillin from 35 % in 2013 to 60 % in 2015, but resistance to amoxicillin, the first line pneumonia treatment, remained low (1 %). Although vaccine-type pneumococci decreased significantly during the study period, the prevalence of residual vaccine-types remained high (21 %). Detection of respiratory syncytial virus or adenovirus were associated with parent-reported rapid or difficult breathing and antibiotic treatment in the past week.

A *qualitative* phenomenographic study was subsequently conducted in urban and rural Moshi in 2019. Individual in-depth interviews with primary healthcare workers showed a reliance on physical examination of the child and history from the mother when deciding whether to prescribe an antibiotic. However, their confidence in providing advice as to non-antibiotic treatment

varied. Most mothers attending the focus group preferred seeking care for their sick child at healthcare facilities, but they faced barriers including unforeseen costs, travel, and lack of support from their husbands. Pharmacies were often perceived as cheap and convenient place to obtain antibiotics for children, whilst some mothers sought health advice from a trusted neighbour.

Conclusions: Increasing resistance to antibiotics and residual vaccine-types require continued epidemiological surveillance of pneumococci in the post PCV13 era. Healthcare workers need support to develop their clinical and consultation skills, meanwhile mothers should be supported in seeking appropriate healthcare for their children. For this, improved equity and increased presence of community health workers are necessary.

Keywords: Antimicrobial stewardship; Drug resistance, Bacterial; Drug prescribing; infant; pneumococcal conjugate vaccines; *Streptococcus pneumoniae*; Tanzania; viruses

SAMMANFATTNING PÅ SVENSKA

Användning av antibiotika samt förekomst av pneumokockbakterier och luftvägsvirus hos barn i Tanzania

BAKGRUND

Antibiotika kan vara livräddande vid allvarliga bakteriella infektioner, men ökad bakteriell resistens är ett hot mot de stora förbättringar som skett i barnadödlighet de senaste decennierna. Då all användning av antibiotika kan bidra till utveckling av resistens, är det av yttersta vikt att antibiotika används på ett ansvarsfullt sätt. Samtidigt som tillgången till antibiotika fortsatt är otillräcklig i många delar av Afrika söder om Sahara, har flertalet tidigare studier visat att det också förekommer överanvändning av antibiotika vid infektioner som läker av sig självt, eller som orsakas av virus där antibiotika inte är verksamt. Detta gäller även i Tanzania, men det är inte klarlagt på en djupare nivå varför antibiotika ofta förskrivs och används på felaktiga grunder hos barn i landet.

Pneumokockbakterier är en vanlig orsak till lunginflammation, men bakterien kan även orsaka hjärnhinneinflammation och blodförgiftning, särskilt hos små barn. Pneumokocker finns ofta i de övre luftvägarna hos barn utan att ge symptom. Den viktigaste orsaken till att pneumokocker kan orsaka svår sjukdom är dess kapsel, ett skyddande hölje som gör det svårare för immunförsvaret att avdöda bakterien. Det finns över 100 olika typer av pneumokocker baserat på skillnader i kapselns struktur. Samtidigt är virus en vanlig orsak till både enklare förkylningar och lunginflammation hos barn, vilket är en utmaning då virusinfektion både kan leda till onödig användning av antibiotika och följas av en svårare bakteriell sjukdom.

I Tanzania introducerades ett nytt vaccin mot pneumokocker 2012. Äldre pneumokockvaccin är inte effektiva hos barn under 2 år, men de nyare vaccinen kopplar ihop beståndsdelar från kapseln till ett bärarprotein vilket bättre aktiverar immunförsvaret hos små barn. Vaccinet ger skydd mot allvarlig sjukdom orsakat av 13 olika pneumokocktyper och skyddar således inte mot alla pneumokockinfektioner. I vissa länder är en hög andel

pneumokocker resistenta mot vanliga typer av antibiotika, t.ex. penicillin, men hur det är i Tanzania efter introduktion av det nya vaccinet är inte känt.

METOD OCH RESULTAT

För att undersöka förekomsten av pneumokocker hos barn och bakteriernas antibiotikakänslighet inkluderades totalt 775 barn under 2 år då de sökt offentlig primärvård för vaccination eller enklare vård i staden Moshi, norra Tanzania mellan 2013 och 2015. Vårdnadshavaren svarade på frågor om barnets hälsa samt familjens sociala och ekonomiska situation, och ett prov togs från barnets bakre näsvägg. Över hälften av barnen hade fått antibiotika de senaste 3 månaderna enligt sin vårdnadshavare, många på grund av snuva eller hosta, vilket indikerar en överanvändning mot infektioner som inte kräver antibiotika för läkning. Odling av pneumokocker visade en ökning av resistens mot penicillin som tas i tablettform eller mixtur, från 35 % 2013 till 60 % 2015. Däremot var resistens mot det något bredare medlet amoxicillin låg (1 %), vilket är förstahandsvalet vid behandling av lunginflammation hos barn enligt Världshälsoorganisationen (WHO). Trots att pneumokocktyper som ingår i det nya vaccinet minskade betydligt under studiens gång, kunde vaccintyper fortsatt påvisas hos 21 % av barnen 2015. Vaccintyper påvisades oftare hos ovaccinerade barn jämfört med dem som var vaccinerade med pneumokockvaccinet. Hos en hög andel av barnen kunde flera olika bakterier och virus påvisas samtidigt i luftvägarna. De barn som hade vissa virus i luftvägarna (RS virus och adenovirus) hade oftare fått antibiotika veckan innan provtagning jämfört med barn utan dessa virus.

För att närmare beskriva användning av antibiotika hos barn i norra Tanzania, utfördes under 2019 intervjustudier både i Moshi stad och på landsbygden. Individuella djupintervjuer utfördes med vårdpersonal som alla förskrev antibiotika till barn, men hade olika utbildning och arbetade både inom offentlig och privat primärvård. De flesta hälsoarbetare baserade sin bedömning om barnet behövde antibiotika på en fysisk undersökning av barnet samt på mödrarnas berättelse. Däremot varierade deras självförtroende i att enbart rekommendera symptomlindrande behandling till barnet då antibiotika inte var nödvändigt. Några hälsoarbetare var tveksamma till om vissa antibiotika var av tillräcklig hög kvalitet. Familjens sociala eller ekonomiska situation kunde också påverka vårdpersonalens val av utredning och behandling, då vissa familjer till exempel inte hade råd att köpa antibiotika om

det inte fanns tillgängligt och gratis på kliniken. Detta ledde till att barn i familjer med låg inkomst i högre utsträckning fick behandling sämre lämpad för den aktuella infektionen.

Vårdnadshavare till barn under 5 år bjöds in till gruppintervjuer i anslutning till primärvårdsbesök, dock var inga fäder närvarande för inkludering. De flesta mödrar föredrog att gå till en primärvårdsinrättning när deras barn blev sjuka, men det fanns betydande barriärer såsom oförutsedda kostnader i samband med besöket och bristande stöd från deras makar. Resor till vårdinrättningen var också ett hinder, särskilt kvälls- eller nattetid. Vissa mödrar hade också upplevt bristande respekt från vårdpersonal i samband med sjukvårdsbesök. Apotek ansågs som ett billigt och enkelt sätt att få tag på antibiotika till barn, även utan recept. Vissa mödrar bad om råd från en betrodd granne angående barnens hälsa.

SLUTSATS

Ökad antibiotikaresistens och hög kvarvarande förekomst av vaccintyper, innebär att det finns ett fortsatt behov av övervakning av pneumokocker även efter introduktion av pneumokockvaccinet i Tanzania. Därtill visar hög förekomst av andra virus och bakterier att enstaka åtgärder enbart till viss del kan minska hög barnadödlighet, men att underliggande problem som påverkar smittspridning, såsom bristande tillgång till rent vatten, behöver förbättras.

Vårdpersonal som förskriver antibiotika inom primärvården behöver stöd i att utveckla sin förmåga att bedöma och ge tillförlitliga råd om lämplig behandling till sjuka barn. De ska också kunna lita på att den antibiotika de förskriver är effektiv. Detta kan åstadkommas genom kollegialt utbyte samt övervakning av bakteriell resistens och kvalitetskontroll av antibiotika. Vårdnadshavare behöver stöttning i när, och var, de bör söka lämplig vård för sina barn. De ska också kunna ha tillit till den vård som ges inom primärvården. För att åstadkomma detta behövs utvecklad infrastruktur, ökad jämlikhet, både i familjer och i det offentliga rummet, samt en förhöjd närvaro av hälsoarbetare i anslutning till hemmen. För att förbättra användning av antibiotika hos barn i Tanzania är därför inte individens beteende det största hindret, utan de bristande strukturer som vidmakthåller ojämlik hälsa.

MUHTASARI MAARUFU WA KISAYANSI

Matumizi ya dawa za antibiotiki na uwepo wa pneumococcal bakteria pamoja na virusi vinavyosababisha matatizo ya kupumua kwa watoto wa Kitanzania

UTANGULIZI

Antibaotiki inaweza kuokoa maisha wakati unapata maambukizi mabaya ya bakteria, lakini kuongezeka kwa usugu wa bakteria ni tishio kwa maboresho makubwa ambayo yamefanyika kuhusiana na vifo vya watoto katika miongo ya hivi karibuni. Kwa kuwa matumizi yote ya antibiotiki yanaweza kuchangia katika ukuaji wa usugu, ni muhimu sana kwamba antibiotiki zitumike kwa uangalifu. Ingawaje upatikanaji wa dawa za antibiotiki, katika maeneo mengi ya Afrika Kusini mwa Jangwa la Sahara bado hazitoshi, tafiti nyingi za awali zimeonyesha pia kuwa kuna matumizi ya kupita kiasi ya antibiotiki kwa maambukizi ambayo hupona yenyewe, au ambayo husababishwa na virusi ambapo antibiotiki haifanyi kazi. Hii inahusu pia nchi ya Tanzania, lakini haijafafanuliwa kwa undani zaidi kwa nini antibiotiki huandikiwa kwa wagonjwa mara nyingi na kutumika kwa misingi isiyo sahihi kwa watoto nchini.

Pneumococcal bakteria ni sababu ya kawaida ya nimonia, lakini bakteria huyu pia anaweza kusababisha homa ya uti wa mgongo (meningitis) na maambukizi kwenye damu (septicemia), hasa kwa watoto wadogo. Pneumococcal bakteria (Pneumococci) mara nyingi hupatikana katika njia ya juu ya mfumo wa upumuaji wa watoto bila kusababisha dalili. Sababu kuu ya pneumococcal bakteria kuweza kusababisha ugonjwa mkali ni kibonge chake (*capsule*), kifuniko cha kinga ambacho hufanya iwe vigumu zaidi kwa mfumo wa kinga kuua bakteria. Kuna zaidi ya aina 100 tofauti za pneumococcal bakteria kwa kuzingatia tofauti katika muundo wa kibonge. Wakati huo huo, virusi ni sababu mojawapo ya mafua (simple colds) na nimonia kwa watoto, ambayo ni changamoto kwa kuwa maambukizi ya virusi yanaweza kusababisha matumizi yasiyo ya lazima ya antibiotiki na kufuatiwa na maambukizi makali zaidi wa bakteria.

Nchini Tanzania, chanjo mpya ya pneumococcal (pneumococcal vaccine) ilianzishwa mwaka 2012. Chanjo za pneumococcal za zamani hazifanyi kazi kwa ufanisi kwa watoto chini ya umri wa miaka 2, lakini chanjo mpya zaidi huunganisha vipengele kutoka kwenye kibonge hadi kwa kibeba protini (carrier protein), ambayo huweza kuamsha vema mfumo wa kinga kwa watoto wadogo. Chanjo hutoa ulinzi dhidi ya ugonjwa mbaya unaosababishwa na aina 13 tofauti za pneumococcal na hivyo hailindi dhidi ya maambukizi yote ya pneumococcal. Katika baadhi ya nchi, asilimia kubwa ya pneumococci ni sugu kwa aina za kawaida za antibiotikisi, kama. penicillin, lakini inakuwaje nchini Tanzania baada ya kuanzishwa kwa chanjo hiyo mpya haijulikani.

MBINU NA MATOKEO

Ili kuchunguza kiwango cha pneumococci kwa watoto na usikivu wa antibiotiki (antibiotic sensitivity) kwa bakteria, jumla ya watoto 775 walio chini ya umri wa miaka 2 walijumuishwa pale walipofika kupata huduma ya afya ya msingi ya umma kwa ajili ya chanjo au huduma ya kawaida mjini Moshi, Kaskazini mwa Tanzania kati ya 2013 na 2015. Mlezi alijibu maswali kuhusu afya ya mtoto na hali ya kijamii na kifedha ya familia, na sampuli ilichukuliwa kutoka kwenye ukuta wa nyuma wa pua ya mtoto. Zaidi ya nusu ya watoto walikuwa wamepokea dawa za antibiotiki katika muda wa miezi 3 iliyopita kulingana na maelezo ya mlezi wao, wengi kwa ajili ya mafua au kikohozi, ikionyesha matumizi kupita kiasi kwa maambukizi ambayo hayahitaji antibiotiki ili kupona. Kipimo cha kuotesha (culture) pneumococci kilionyesha kuongezeka kwa usugu dhidi ya penicillin iliyochukuliwa katika vidonge au kama dawa ya maji iliotumika kutumia kupitia mdomoni, kutoka 35% mwaka 2013 hadi 60% mwaka wa 2015. Kinyume chake, usugu dhidi ya dawa yenye uzio mpana kiasi ya amoxicillin ilikuwa ndogo (1%), ambayo ni tiba ya mstari wa kwanza ya nimonia kwa watoto kulingana na Shirika la Afya Duniani (WHO). Ingawa aina za pneumococcal zilizojumuishwa katika chanjo mpya zilipungua kwa kiasi kikubwa wakati wa utafiti, aina za chanjo (vaccine type) bado ziliweza kugunduliwa katika 21% ya watoto mwaka wa 2015. Aina za chanjo ziligunduliwa mara nyingi zaidi kwa watoto ambao hawajachanjwa ikilinganishwa na wale waliopata chanjo ya pneumococcal. Katika asilimia kubwa ya watoto, bakteria na virusi kadhaa tofauti katika mfumo wa upumuaji ziliweza kugunduliwa kwa wakati huo huo. Watoto ambao walikuwa na virusi fulani katika mfumo wa upumuaji (RS virus na

adenovirus) mara nyingi walipewa antibiotiki katika wiki moja kabla ya sampuli kuchukuliwa ikilinganishwa na watoto wasio na virusi hivi.

Ili kuelezea zaidi matumizi ya antibiotiki kwa watoto Kaskazini mwa Tanzania, tafiti za usaili zilifanyika mwaka 2019 katika maeneo ya Moshi mjini na vijijini. Mahojiano ya kina ya mtu binafsi yalifanywa kwa wahudumu wa afya, ambao wote waliwaandikia watoto antibiotiki lakini walikuwa na mafunzo tofauti na walifanya kazi katika huduma za afya ya msingi za umma na za kibinafsi.
Wahudumu wengi wa afya walizingatia tathmini zao endapo kama mtoto alihitaji dawa za antibiotiki kwa uchunguzi wa kimwili wa mtoto na vilevile kutokana na historia ya mama. Kwa upande mwingine, imani yao ilitofautiana katika kupendekeza matibabu ambayo yatapunguza dalili peke yake kwa mtoto wakati antibiotiki haikuwa lazima. Baadhi ya wahudumu wa afya walikuwa na mashaka iwapo baadhi ya antibiotiki zilikuwa za ubora wa juu wa kutosha. Hali ya kijamii au kiuchumi ya familia inaweza pia kuathiri uwezo wa mhudumu wa afya katika kuchagua uchunguzi na matibabu, kwani baadhi ya familia, kwa mfano, hazingeweza kumudu kununua antibiotiki endapo hazikuwepo au hazikutolewa bure katika kliniki. Hii ilipelekea watoto kutoka familia zenye kipato cha chini mara nyingi zaidi kupewa matibabu yasiyofaa sana kwa maambukizi husika.

Walezi wa watoto chini ya umri wa miaka 5 walialikwa kwenye mahojiano ya kikundi kuhusiana na ziara katika afya ya msingi, hata hivyo, akina baba hawakuwepo ili washirikishwe. Akina mama wengi walipendelea kwenda kwenye kituo cha huduma ya afya ya msingi pindi watoto wao walipougua, lakini kulikuwa na vikwazo vikubwa kama vile gharama zisizotarajiwa na zinazohusiana na ziara hiyo na ukosefu wa usaidizi kutoka kwa waume zao. Kusafiri kwenda kwenye kituo cha afya pia ilikuwa kikwazo, haswa jioni au usiku. Baadhi ya wakina mama pia walikuwa wamekumbana na ukosefu wa heshima kutoka kwa wahudumu wa afya kipindi cha ziara hizo za afya. Maduka ya dawa (pharmacies) yalionekana kuwa njia nafuu na rahisi ya kupata antibiotiki kwa watoto, hata bila kuandikiwa na mtoa huduma ya afya (prescription). Baadhi ya wakina mama walitafuta ushauri kutoka kwa jirani wanayemwamini kuhusu afya za watoto wao.

HITIMISHO

Ongezeko la usugu wa antibiotiki na wingi wa mabaki yatokanayo na aina za chanjo kunamaanisha kuwa kuna uhitaji endelevu wa ufuatiliaji wa kina wa pneumococcal (pneumococcal surveillance) hata baada ya kuanzishwa kwa chanjo ya nimonia (pneumococcal vaccine) nchini Tanzania. Zaidi ya hayo, kiwango kikubwa cha virusi vingine na bakteria zinaonyesha kuwa afua (intervention) moja inaweza tu kupunguza vifo vingi vya watoto kwa kiasi fulani, lakini kwamba matatizo ya msingi yanayoathiri kuenea kwa maambukizi, kama vile ukosefu wa maji safi, yanahitaji kuboreshwa.

Wahudumu wa afya wanaotoa (precsribe) antibiotiki katika huduma za afya za msingi wanahitaji usaidizi katika kukuza uwezo wao wa kutathmini na kutoa ushauri wa kuaminika juu ya matibabu sahihi kwa watoto wagonjwa. Pia wanapaswa kuwa na uwezo wa kuamini kwamba antibiotiki wanazozitoa zina ufanisi. Hili linaweza kufanikiwa kupitia elimu ya rika-kwa-rika na vile vile kwa ufuatiliaji wa usugu wa bakteria na udhibiti wa ubora wa antibiotiki. Walezi wanahitaji usaidizi wa in wakati, na wapi, wanapaswa kutafuta huduma inayofaa kwa watoto wao. Wanatakiwa kuwa na uwezo wa kuamini huduma inayotolewa ndani ya afya ya msingi. Ili kufanikiwa hili, miundombinu iliyoendelezwa, kuongezeka kwa usawa, kote katika familia na katika maeneo ya umma, pamoja na kuongezeka kwa uwepo wa wafanyakazi wa afya ya jamii kunahitajika. Kwa hiyo, ili kuboresha matumizi ya antibiotiki kwa watoto nchini Tanzania, kikwazo kikubwa sio tabia ya mtu binafsi, bali mapungufu kwenye miundo ambayo inaendeleza afya isiyo sawa.

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CONTENT

ABBREVIATIONS

ADDO	Accredited drug-dispensing outlets
AMR	Antimicrobial resistance
CHW	Community Health Worker
Ct	Cycle threshold
FGD	Focus group discussion
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency viruses
IDI	Individual in-depth interviews
IMCI	Integrated Management of Childhood Illness
IPD	Invasive pneumococcal disease
KCMC	Kilimanjaro Christian Medical Centre
LRTI	Lower respiratory tract infection
MDG	Millennium Development Goal
MIC	Minimal inhibitory concentration
NVT	Non-vaccine-type (pneumococci)
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PPSV	Pneumococcal polysaccharide vaccine
RSV	Respiratory syncytial virus
SDG	Sustainable Development Goal

UN	United Nations
UNICEF	United Nations Children's Fund
URTI	Upper respiratory tract infection
VT	Vaccine-type (pneumococci)
WHO	World Health Organisation

1 INTRODUCTION

In the past two decades, global child mortality has been reduced by around half. Nevertheless, an estimated 5 million children in 2019 did not live to until their fifth birthday.[1] The year 2015 marked the end of the Millennium Development Goals (MDGs), and a new framework for development was adopted by the United Nation (UN) member states, namely the Sustainable Development Goals (SDGs). The SDG 3.2 on child health aims to:

"By 2030, end preventable deaths of newborn babies and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births."[2]

Reductions in neonatal mortality have been slower compared to total under-5 mortality and, in consequence, the leading cause of death in children globally are neonatal disorders. Outside of the neonatal period, lower respiratory tract infections (including bronchiolitis and pneumonia) followed by diarrhoea, are the leading causes of death.[1] Malnourishing increases children's vulnerability to infectious disease[3] and thus contributes to mortality.

The relative inequity in distribution of child deaths has grown in the past three decades with 51 countries in Asia and sub-Saharan Africa now accounting for 80 % of all child mortality.[1] To reach the SDG 3.2, the average decline in child and neonatal mortality in these countries will need to double by 2030.[4] Many of these nations also face large inequalities within the country, related to rural versus urban infrastructure, education, and ethnicity.

1.1 UNITED REPUBLIC OF TANZANIA, KILIMANJARO REGION

During the post-colonial era, Tanzania has largely enjoyed peace and socio-political stability. The population was approximately 63.5 million in 2021, with around 45 % of the population living below 2.15 US dollar per day, internationally considered as extreme poverty.[5] Despite rapid population growth, Tanzania still has declining poverty rates and has been recognised as a lower-middle-income country.

Meanwhile, Tanzania is among the top ten countries with the highest burden of deaths due to pneumonia and diarrhoea in children.[6] In 2019, all-cause neonatal and under-5 mortality rates were around 20 and 50 per 1000 live births, respectively.[7]

Figure 1. Map of Moshi Municipal (urban) and District (rural) Councils, Kilimanjaro Region, United Republic of Tanzania.

Moshi Municipal (urban) and Moshi District (rural) Council are situated in the Kilimanjaro Region of Northern Tanzania (Figure 1). Due to its high altitude, Kilimanjaro Region has a low incidence of malaria.[8] In urban and rural Moshi, key economic activities include farming and trading in primary produce whilst in urban Moshi small retail outlets and tourism are also common sources of income. Poverty incidence in Kilimanjaro region is among the lowest in the country according to national estimates.[9]

1.2 INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS

In the mid 1990s, in order to improve the performance of healthcare workers at first-level healthcare facilities in low- and middle-income countries, the WHO/UNICEF together with partners developed the clinical guidelines, Integrated Management of Childhood Illness (IMCI).[10] Instead of applying disease-specific programs they sought to train and support healthcare workers in improving the provision of care for pneumonia, diarrhoea, measles, malaria, HIV, malnutrition, and anaemia.[11] Training included the following: recognising danger signs that indicates need of urgent referral after essential treatment; classifying illnesses that may be treated at home; and providing counselling for mothers on drug administration, feeding and follow-up.[10]

Training in IMCI has been carried out in many parts of the world, including Tanzania, and an early, comparative evaluation of IMCI implementation in southern Tanzania showed promising results in relation to child mortality.[12] However, later studies have shown poor adherence to guidelines by healthcare workers[13, 14] and barriers to implementation consisting of low initial education and lack of regular support after training.[15] Reviews show the IMCI may lead to fewer deaths in children under-5, but the evidence in support of this is limited.[16] Meanwhile, the causes of mortality and morbidity in children have changed greatly since development of the IMCI whilst no updates have been made since 2014, thus a substantial revision are being called for.[17] Furthermore, whereas the IMCI program also aimed to improve health care systems and community practice relating to childhood illness, implementation of these parts of the program has been lacking.[18]

1.3 ACUTE RESPIRATORY TRACT INFECTIONS

The respiratory tract may be divided into the upper respiratory tract (nasal cavity, naso- and oropharynx, and larynx) and the lower respiratory tract (trachea, bronchi, and lung tissue) (Figure 2). Most episodes of upper respiratory tract infections (URTI), including rhinitis and pharyngitis, are caused by viruses. Whilst children under 6 months and breastfeeding infants are partly protected by maternal antibodies, children from 6 months up to the age of 5 years are frequently affected by URTI. However, viruses causing uncomplicated URTI in older children may in neonates (<4 weeks) or infants (<1 year) be more complicated due to, for example, more loose or permeable mucosal membranes and narrow airways.

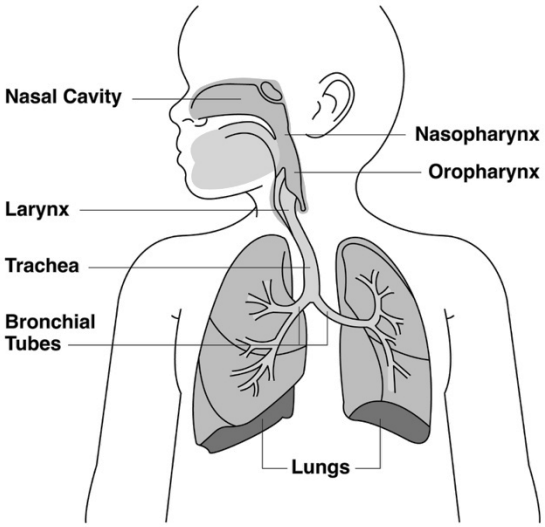


Figure 2. The respiratory tract.

Lower respiratory tract infections (LRTI) include, as stated above, bronchiolitis and pneumonia. Bronchiolitis involves inflammation of the small airways[19] whilst pneumonia affects the lung tissue, including the alveoli which facilitates the gas exchange involved in breathing.[20] Pneumonia may, in turn lead to local complications (including pleural effusion and necrosis) and

systemic complications (including bacteraemia and sepsis).[21] Whilst the definition and classification of pneumonia are the subject of debate,[20] radiology has often been used to confirm pneumonia diagnosis in studies.[22, 23] According to the IMCI, children presenting with cough or difficulty breathing are assessed for possible pneumonia.[11] If a child presents with wheezing (indicating asthma or bronchiolitis), an inhaled rapid acting bronchodilator should be administered if available. For children presenting with chest indrawing or rapid breathing (2 – 12 months; ≥50 breaths/minute, 12 months – 5 years; ≥40 breaths/minute), a 5-day course of oral amoxicillin, considered first-line antibiotics for childhood pneumonia, are recommended. If the child is presenting with any of the danger signs (unable to eat/drink, lethargic or has convulsions) or stridor, an initial dose of antibiotics is administered before referring the child to hospital. However, the IMCI pneumonia diagnosis have, in practice been shown to lead to overdiagnosis of pneumonia and under-diagnosis of wheezy chest disease,[24, 25] thus contributing to inappropriate antibiotic use.[22] Recent studies shows that availability of inhaled rapid acting bronchodilators is relatively good in Tanzania,[26] but the cost may still be present a barrier to use (around 5USD).[27]

Introduction of conjugate vaccines for *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* have largely changed the clinical outcome and aetiology of childhood pneumonia.[28] However, development of disease depends on a complex interaction between pathogen and the child's immune defence, which may be affected by environmental factors such as household air pollution.[29-33] Risk factors for development of childhood pneumonia include the following: low birth weight; lack of exclusive breastfeeding; household air pollution; parental smoking; under-nutrition; HIV and incomplete or inadequate vaccination.[28, 34]

1.4 AETIOLOGY OF RESPIRATORY TRACT INFECTIONS

Whilst bronchiolitis is almost always caused by virus,[19, 20] determining the aetiology of pneumonia is notoriously difficult. As the site of infection, i.e. the lung tissue, cannot usually be sampled, microbiological test analysis has to be carried out on samples that may not be representative for the infection.[35] This includes the upper respiratory tract which, especially in children, is inhabited by a wide range of commensal microorganisms (such as viridans streptococci) and transient pathogenic bacteria.[36] Although the lower respiratory tract is no longer considered 'sterile', development of lower respiratory tract infections involves micro aspiration of pathogens from the upper respiratory tract and failure of eradication.[37] However, bacteria obtained from the upper respiratory tract, in cases of childhood pneumonia, may not by default be the one(s) causing the disease.[36]

Several viruses are associated to both upper and lower respiratory tract infections in children. Among these are rhinovirus, the cause of around 50 % of all URTIs in children, but also recognised as the second most common cause of viral bronchiolitis in children.[38] Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis in children but has since the introduction of conjugate vaccines been recognised as the most common pathogen associated to severe pneumonia in children in Asia and Africa.[23] However, adults and older children with RSV infection may only present with URTI.[39] Human metapneumovirus may cause similar clinical features as RSV, with a significant burden of hospital admissions especially in infants.[40, 41] Influenza A and B are strongly associated with fever in children,[22] symptoms from the upper respiratory tract are common and these viruses may also cause LRTI.[23, 42] Parainfluenza virus is the most common cause of croup in children, and is further associated to both URTI and LRTI.[43, 44] Adenovirus may cause a wide range of symptoms in children including URTI.[45, 46] However, less is known about its share in LRTI but it has been associated to the rare complication of bronchiolitis obliterans i.e. fibrosis of the small airways.[47] Non-polio enteroviruses are the main cause of aseptic meningitis in children.[48] They are also common in URTI and one serotype has been associated to LRTI.[49] Coronavirus represents a group of viruses of which the SARS-CoV-2 were responsible for the recent pandemic during which children were relatively

spared from severe LRTI.[50] As a group, coronaviruses are most common in URTI but is an uncommon cause of LRTI in children.[23, 51]

It is well-known that viral respiratory infections predispose children to secondary bacterial infections, often with a more severe clinical course.[52] There are several reasons for this, including upregulated receptors on epithelia during viral infection which increases the adhesion of bacteria[53] and impaired mucociliary capacity leading to reduced mechanical clearance of pathogens.[52] Furthermore, the release of catecholamines and cytokines provoked by inflammation might alter gene expression and enhance virulence in certain bacteria.[37] The most well-established interaction is that of influenza infection leading to subsequent pneumococcal pneumonia,[37, 54] thought to be the main reason for the majority of deaths during the 1918 influenza pandemic.[55]

Bacteria involved in LRTI include, but are not restricted to, *Bordetella pertussis*, responsible for the coughing disease, pertussis, or whooping cough, that may be fatal in young infants.[56] Worldwide immunization since the 1980s has reduced the number of cases although outbreaks still occur. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may cause so-called atypical, or non-lobar pneumonia, more often in school-aged children.[57, 58] Where conjugate vaccine against *H. influenzae* type b (Hib) is used with high coverage, invasive disease in children is very rare[59] but both *H. influenzae* type b and non-type b (including non-encapsulated) still contribute to cases of childhood pneumonia[23] and non-encapsulated *H. influenzae* are common in *otitis media*.[60, 61] Furthermore, the pathogen which is the focus of this thesis, *S. pneumoniae*, will be described in greater detail below.

1.5 *STREPTOCOCCUS PNEUMONIAE*

S. pneumoniae, or the pneumococcus, is an important human pathogen. Young children, the elderly and the immunocompromised are among those most susceptible to pneumococcal disease. The pneumococci are frequently detected in the nasopharynx of preschool children. Whilst most acquisitions do not result in manifest disease, carriage may lead to disease such as *otitis media* and pneumonia, or invasive pneumococcal disease (IPD) including sepsis, and meningitis. Globally in 2018, pneumococci were responsible for an estimated 300 000 deaths in children under five years of age, with the highest death toll occurring in African children.[59] Hence, pneumococci are the pathogen associated with the highest number of deaths in children.[62] Around 80 % of children dying from pneumococcal infections presented with pneumonia.[59]

Although there are non-typeable or non-encapsulated strains of pneumococci, the polysaccharide capsule is the most important virulence factor of this Gram-positive, diplococcus bacterium. In fact, there are over one hundred different types of pneumococci based on alterations in the capsule.[63-65] Traditionally, these are called serotypes or serogroups, as the classification are based on serological methods, but they reflect differences in genes coding for the capsule. Moreover, different serotypes may be prone to either establishing long duration of carriage, or shorter carriage but with higher probability of causing invasive disease.[66] Prior to worldwide implementation of pneumococcal conjugate vaccines (described below), serotypes associated to high probability of invasive disease once acquired were 1, 4, 5, 7, 9V, 14 and 18C whilst serotype 3, 6A, 6B, 15BC, 19 and 23 were associated to lower invasiveness.[67-68] However, highly prevalent serotypes with a low probability of causing invasive diseases were, in some cases found in invasive diseases to the same extent as more invasive ones.[69] Pneumococci are capable of horizontal gene transfer, i.e. they may obtain new genes from other streptococcal species. This is important in capsular switching and in the development of resistance to antibiotics and among pneumococci.[70, 71]

1.6 PNEUMOCOCCAL CONJUGATE VACCINES

Pneumococcal polysaccharide vaccines (PPSVs) have been available since the 1980s. However, this preparation fails to immunize infants and toddlers who are at highest risk of pneumococcal disease.[72] Pneumococcal conjugate vaccines (PCVs) were therefore developed to induce an effective and lasting immune response in children under two years of age. The antigen consists of a pneumococcal polysaccharide, specific for each serotype, conjugated to a carrier protein. In consequence, the vaccine provides protection for the included serotypes, or vaccine-types (VT). The first PCV targeted 7 different serotypes (Table 1); however, several serotypes important in IPD in Africa, Asia and South America were not included.[73] Additionally, non-vaccine-type (NVT) pneumococci, such as 19A, were making a significant contribution to disease in countries already implementing the PCV7.[74] Therefore, higher valent pneumococcal conjugate vaccines including three (PCV10) or six (PCV13) additional serotypes were developed and have been implemented worldwide (Figure 3). Furthermore, the PCV15 and PCV20 have currently being licensed for adults in the U.S.[75]

Table 1. Pneumococcal conjugate vaccines (PCVs) and their respective serotypes.

	Serotypes
PCV7 (Prevnar 7)	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10 (Synflorix/PNEUMOSIL)	+ 1, 5, 7F
PCV13 (Prevnar 13)	+ 3, 6A, 19A
PCV15 (Vaxneuvance)	+ 22F, 33F
PCV20 (Prevnar 20)	+ 8, 10A, 11A, 12F, 15B

PCV: Pneumococcal conjugate vaccine

The PCV10 and PCV13 have proved to provide protection from IPD, and radiology confirmed pneumonia in both high-income and low- and middle-income countries.[76] As in Europe,[77] studies in the Gambia and Malawi have reported at least a 50 % reduction in cases of IPD in pre-school children three to seven years after introduction of the PCV13.[78, 79] Furthermore, in the Gambia, significant reductions in severe, or pneumococcal pneumonia in

children were observed, whilst reductions in hospital requiring or radiology confirmed childhood pneumonia were smaller.[80] However, surveillance of microbiological verified or invasive disease is rare in sub-Saharan Africa. Therefore, analysing residual VT and NVT pneumococci in the nasopharynx is a useful surrogate when monitoring impact of the vaccine.[81]

In December 2012 the PCV13 were introduced into the national child immunization program in Tanzania.[82] The PCV program is funded by Gavi, the Vaccine Alliance, representing approximately 1/3 of the total support from Gavi in 2020.[83] The vaccine is given to infants at 6, 10 and 14 weeks with no booster dose, also referred to as a 3+0 schedule.

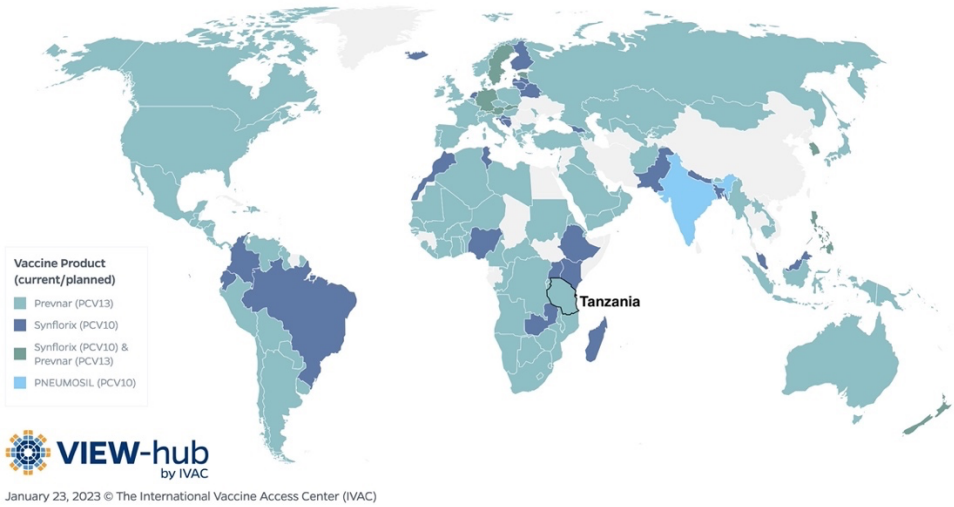


Figure 3. Worldwide implementation of the pneumococcal conjugate vaccine (PCV). (Printed with permission.)

1.7 ANTIMICROBIAL RESISTANCE

Antibiotics have saved countless of lives since the 1940s and are a foundation for modern medicine. However, the ability of bacteria to develop resistance to antibiotics was already predicted by Sir Alexander Fleming, who had discovered penicillin, himself.[84] Antimicrobial resistance (AMR) includes resistance to antivirals, antifungals, and antibiotics. This term is often used interchangeably with antibiotic resistance, which refers only to bacteria resistant to antibiotics.[85] Although some bacterial species are inherently resistant to certain antibiotics, it is the selective pressure induced by antibiotics that has given rise to the increased prevalence of resistant bacteria seen worldwide. In fact, the association between antibiotic consumption and resistance is supported by several studies at different levels including individuals,[86] communities[87-89] and nations.[90] Around 90 % of all antibiotics are used in the community making this the most important target for improved antibiotic stewardship.[91]

Bacteria can gain resistance to antibiotics through de-novo mutations or, by incorporating new genetic material into their genome. Sub-lethal concentrations of antibiotics may contribute to these adaptive processes.[92] Bacteria that have gained resistance to antibiotics may, at times lose fitness but, in general, they do not become more pathogenic.[85] However, once an infection is established, it becomes more difficult to treat. While antibiotics enhance the selection of resistant bacteria, the likelihood of *transmission* of resistant strains or gene elements is higher in crowded areas lacking in sanitation and clean water.[93] As a result, low- and middle-income countries with poor infrastructure are more vulnerable to bacterial antimicrobial resistance, thus highlighting that improved use will not be the sole solution in these countries.

Significantly, antibiotics are not only used in humans, but also in livestock and agriculture to improve growth and outcome. In order to combat antimicrobial resistance a *One health* approach has thus been called for.[94, 95] This has been recognised by the WHO in the global action plan on antimicrobial resistance, outlining the following five main objectives: 1) to raise awareness, 2) to improve knowledge through surveillance and research, 3) to reduce incidence of infection through improved sanitation, hygiene, and other preventive measures 4) to optimize use of antimicrobials and 5) to develop an economic

case for investment in medicines, vaccines or diagnostic tools that will benefit all countries.[96] Furthermore, countries were urged to implement a national action plan on antimicrobial resistance which was achieved by Tanzanian authorities in 2017.[97]

In paradox, access to antibiotics remains a challenge in poor and rural areas of low- and middle-income countries. A recent study on global antibiotic consumption in low- and middle-income countries indicated the highest use in eastern Europe, central Asia, and parts of southeast Asia whilst lowest use was estimated for sub-Saharan Africa.[98] However, surveillance capacity relating to antibiotic use in sub-Saharan Africa is lacking and thus relies mainly on community surveys.[98, 99] A cross-sectional study conducted in Tanzania 2006-2016 estimated that around 80 % of children attending a healthcare facility for a respiratory illness were prescribed an antibiotic.[100] Further, a study in urban Moshi including children hospitalised with community-acquired pneumonia during 2017 showed that around a quarter of the children had received unprescribed or leftover antibiotics prior to admission.[101] This indicates high use in Tanzanian children, also in the Kilimanjaro region.[101, 102] A recent study shows the global burden of all-age deaths associated or attributable to bacterial antimicrobial resistance is highest in sub-Saharan Africa.[103] Increasing prevalence of resistant bacteria combined with the high burden of infectious diseases and low access to second- and third-line antibiotics, are contributing factors.

In order to assist countries when developing strategies for antibiotic stewardship, the WHO has divided antibiotics used for children into three different categories in the 'WHO Model list of essential medicines for children' in 2017.[104] The first is the 'access' group, antibiotics that should be widely available, affordable, and quality-assured (for example beta-lactam antibiotics). Secondly, the 'watch' group antibiotics include antibiotics with high resistance potential that should be prioritized in stewardship programs (for example macrolides and fluroquinolones). Lastly, the 'reserve' group antibiotics, such as 4th and 5th generation cephalosporines, are considered last resort treatment.

1.8 STRUCTURE OF HEALTHCARE AND AVAILABILITY OF ANTIBIOTICS IN KILIMANJARO REGION

In Kilimanjaro region, around 90 % of the population is estimated to live within five kilometres of a healthcare facility.[105] Primary healthcare consists of dispensaries, and more well-equipped healthcare centres.[106] The majority are public, but some are also private or run by faith-based organizations.[107] Children under the age of five are endorsed by a 'no fee health service policy' at public healthcare facilities.[108]

There is a critical deficit of educated healthcare workers, globally, and in Tanzania. The WHO has recognised community health workers (CHW) as vital for bridging this gap, to reach disadvantaged populations and enhance disease prevention.[109, 110] In Tanzania, CHWs have been supporting community mobilization programmes on a voluntary basis for decades.[111] Although efforts have been made to formalize their training, pay salaries and integrate them into the formal healthcare system, the vast majority functioning in the community are still volunteers.[27]

Community pharmacies, including type 1 pharmacies and accredited drug-dispensing outlets (ADDOs), are legally permitted to sell and dispense a limited list of prescription-only medicines, such as amoxicillin.[112, 113] The ADDO program was designed to ensure availability of quality medicines and services in rural areas of Tanzania where public healthcare centres may be far away for people to reach.[112] However, ADDOs are abundant in urban areas, including Moshi, where access to healthcare facilities is better in terms of distance.[113] Previous studies of dispensers and drug-shop owners in community pharmacies across Tanzania and in the Kilimanjaro region shows that antibiotics are often sold or dispensed on patient demand, i.e. without prescription from a healthcare worker.[113-118]

2 AIM

The overall aim of this thesis was to describe the epidemiology of *S. pneumoniae* and other respiratory pathogens in the post PCV13 era and to further describe the experiences of antibiotic use in Tanzanian children among prescribing primary healthcare workers and parents/guardians.

The specific aims were:

- To describe the antibiotic susceptibility and serotype distribution of pneumococci carried by Tanzanian children after introduction of the PCV13 (Paper I and II)
- To identify socioeconomic and/or health factors associated with detection of pneumococci or other respiratory pathogens in children under two years of age in Tanzania (Paper I and II)
- To describe the experiences of primary healthcare workers in prescribing antibiotics to children under five years of age attending primary health care in Moshi, Tanzania (Paper III)
- To describe the experiences of parents or guardians residing in Moshi, Tanzania, of antibiotic use in children under five years of age (Paper IV)

3 METHODS

For this thesis, both quantitative and qualitative methods have been applied. Typically, in medical research, quantitative methods have predominated .[119] In general, these focus on *explaining* phenomena by measuring, counting, and testing hypotheses. The data are typically numeric and thus facilitate statistical analysis. Qualitative research was developed within social and human science and involves theories of interpretation (hermeneutics) and human experience (phenomenology). The attention focuses rather on *understanding* phenomena, using tools such as observations or in-depth interviews. The data derived are mainly textual; analysis is performed in a structured manner with a focus on either describing, interpreting, or generating hypothesis.[120] Qualitative studies are sensitive to contextual factors and require that the researcher should be open and reflective as to the way he or she may influence the knowledge production. Qualitative and quantitative methods have often been described as two contrasting cultures, and cross-cultural communication has been marked by misunderstandings.[121] However, they have also been described as complementing each other in medical research[119] as combining the methods may enrich the description of a phenomenon, just as a landscape looks very different if viewed from the air or from the ground. The term, 'triangulation' originates from a method used by land surveyors in which the validity of a map increases if measurements are taken from different angles. In research, triangulation may increase the validity of the research if agreement is reached among different sources or methods.[120]

3.1 STUDY SETTING AND TRAINING

The studies were conducted in the Kilimanjaro region of Northern Tanzania. Primary healthcare facilities, chosen to represent different geographical and socioeconomic parts of Moshi Municipal (urban) and Moshi District (rural) council, were included (Table 2).

Table 2. Study sites and time of data collection.

	Year	Month[b]	Level of primary healthcare facility (*n*)	Owner (*n*)	District (*n*)
Quantitative study (paper I and II)	2013[a]	October-November	Dispensary (2) Health Centre (1)	Public (3)	Moshi urban (3)
	2014	February-March	Dispensary (2) Health Centre (1)	Public (3)	Moshi urban (3)
	2015[a]	February-March	Dispensary (2) Health Centre (1)	Public (3)	Moshi urban (3)
Qualitative study (paper III and IV)	2019	September - November	Dispensary (7) Health Centre (5)	Public (8) Private (3) Faith-based (1)	Moshi urban (8) Mochi rural (4)

[a]The same study sites were included in 2013 and 2015.

[b]In Northern Tanzania July-October are considered dry season. Early (or long) rainy season extends from March-May and late (or short) rainy season is approximately in November, although climate change has largely changed the predictability of these rainy periods.[122]

For the quantitative data collection, two experienced community health nurses employed at the Community Health Department at Kilimanjaro Christian Medical Centre (KCMC) were appointed. Staff at the Clinical Laboratory at KCMC were trained to perform the laboratory work according to the research protocol. For each year Swedish medical students, including the author in 2014, were recruited to assist in data collection and laboratory work, all students having received training prior to arrival in Tanzania. For the qualitative study, three local research assistants were appointed by an experienced social scientist. The team members were trained in the background, design and qualitative methodology by the author and research team supervisors.

Figure 4. Sister Celina Mayo outside one of the study sites in urban Moshi. As a senior experienced community health nurse, Sister Celina was part of the data collection teams for both the quantitative and qualitative studies. (Published with permission, Johan Franzén (photographer) and Celina Mayo).

3.2 QUANTITATIVE METHODS (PAPER I AND II)

3.2.1 STUDY POPULATION

An epidemiological study including children under two years of age, was performed through repeated cross-sectional surveys in 2013, 2014 and 2015. National child immunization coverage provided by WHO/UNICEF[123] revealed that almost all families in Tanzania attended routine care for their children. Therefore, it was considered viable to include children representing the general child population at primary healthcare facilities providing these services (Table 2). All children under two years of age accompanied by their parent or guardian (>18 years) attending the facility mainly for growth monitoring and vaccination, or the out-patient clinic (for minor illnesses), were invited to participate in the study. Due to the age criteria the same individual children were not likely to be included twice although the same study sites were visited in 2013 and 2015. The parent or guardian responded to a questionnaire involving socio-demographic and health information about the child. All structured interviews were carried out in Kiswahili. The questionnaire was originally developed in 2013 by the medical students and their supervisors and was tested on two mothers visiting KCMC with their children prior to start of the study. Recent use of antibiotics in the child was explored in detail. If the child's medical log was available this was reviewed as a compliment to provide information concerning prescribed antibiotics. A detailed description of the study population is shown in paper I.

3.2.2 CULTURE AND ANTIBIOTIC SUSCEPTIBILITY TESTING OF *S. PNEUMONIAE*

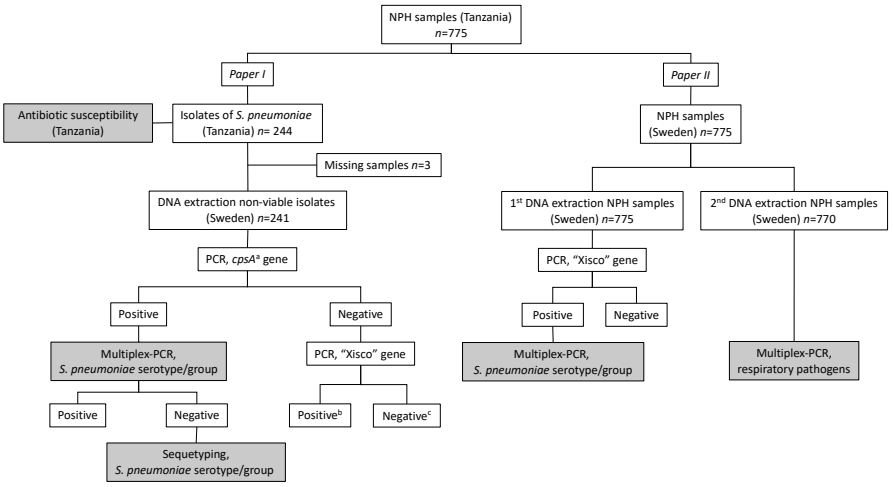
A nasopharyngeal sample was collected from all included children (*n*=775). The samples were transported to the Clinical Laboratory at KCMC and inoculated on agar plates within 6 hours. Identification of grown *S. pneumoniae* was based on colony morphology and optochin sensitivity. Antibiotic susceptibility was determined by disc-diffusion and E-tests, following the procedures and breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[124] Oxacillin was used to screen for β-lactam resistance, if the disc clearance zone was less

than 20 mm the minimal inhibitory concentration (MIC) was determined by E-tests for benzylpenicillin, ampicillin, and ceftriaxone. After pure culturing, all pneumococcal isolates were dissolved in storage medium and stored frozen along with the remaining nasopharyngeal samples at KCMC, awaiting further transportation to the Department of Infectious Diseases, University of Gothenburg, Sweden.

3.2.3 DETECTION AND SEROTYPING OF S. PNEUMONIAE BY MOLECULAR METHODS

Upon arrival in Gothenburg, all pneumococcal isolates were found non-viable. Serotype/group identification was thus performed using molecular based methods both on the non-viable isolates kept in storage medium (paper I) and directly on the nasopharyngeal samples (paper II). The procedures for serotype/group identification varied between the non-viable isolates and nasopharyngeal samples due to a higher concentration of pneumococcal DNA in the storage medium containing non-viable, pure cultured pneumococci (Figure 5). For all polymerase chain reaction (PCR) analyses performed for serotype/group identification, a Cycle threshold (Ct) of <40 was considered positive.

For the non-viable isolates (paper I), a real-time quantitative PCR was initially performed including the *cpsA* gene, coding for the pneumococcal capsule.[126] The *cpsA*-positive isolates were further analysed by a multiplex real-time PCR published by Centres for Disease Control and Prevention (CDC). The method was developed and validated in-house. This method is able to detect all the PCV13 vaccine-type (VT) pneumococci, namely, 1, 3, 4, 5, 6ABCD, 7FA, 9AV, 14, 18, 19A, 19F, 23F, and some non-vaccine-types (NVTs) (2, 7BC/40, 8, 9NL, 10A, 11AD, 12AF/44/46, 15BC, 17F, 20, 22AF, 25AF/38, 33AF/37). For *cpsA*-positive samples that could not be serotyped by the multiplex PCR, a modified 'Sequetyping' protocol was performed.[126] The isolates negative for the pneumococcal capsule were tested for presence of the 'Xisco' gene, a reliable marker for *S. pneumoniae* including non-typeable (or non-capsulated) strains.[127]



NPH; nasopharyngeal, PCR; polymerase chain reaction

[a]The *cpsA* gene is coding for the pneumococcal capsule whilst the 'Xisco' gene is found in both encapsulated and non-typeable pneumococci.

[b]'Xisco' positive samples were confirmed to be non-typeable or non-encapsulated by presence of the *aliC/aliD* gene and further lack of the *cpsB* gene (125).

[c]'Xisco' negative samples were also tested for the bacteria specific 16S gene to confirm lack, or degradation, of bacterial DNA.

Figure 5. Overview of the analysis performed in paper I and II.

The nasopharyngeal samples in paper II were initially analysed for presence of pneumococci as determined by the 'Xisco' gene. Positive samples were analysed by the above-mentioned multiplex real-time PCR for identification of serotypes/groups.

3.2.4 DETECTION OF RESPIRATORY PATHOGENS

The nasopharyngeal samples were also analysed by another multiplex real-time PCR for detection of 14 different viruses (adenovirus, coronavirus 229E, HKU1, NL63 and OC43, influenza A and B, human metapneumovirus, parainfluenza 1–3, rhinovirus, enterovirus, and respiratory syncytial virus (RSV)) and 4 different bacterial species (*Bordetella pertussis*, *Chlamydia pneumoniae*, *H. influenzae* and *Mycoplasma pneumoniae*).[128] A Ct-value of <40 was considered positive. The method could not fully separate rhinovirus and enterovirus due to their almost identical genome. These were therefore grouped together in the analysis.

3.2.5 STATISTICAL METHODS

Univariable and multivariable analyses were performed to explore associations between socioeconomic or health risk factors and detection of *S. pneumoniae* (by culture or PCR). The significance of coefficients was tested for using Wald's test. Univariable and multivariable analyses were also performed to determine associations between parent-reported symptoms or antibiotic use in the children and presence of respiratory pathogens (detected in >20 children). Differences in prevalence of individual serotypes/groups, PCV13 vaccine-type and non-vaccine-type pneumococci between the years and in relation to PCV13 status were examined by Fisher's exact test. The associations between pneumococcal load and presence of other respiratory pathogens (detected in >20 children) were calculated with a two-tailed, Mann-Whitney U test. *P*-values ≤0.05 were considered significant in all analyses. Adjustment for multiple testing was performed by Holm's procedure.

3.3 QUALITATIVE METHODS (PAPER III AND IV)

3.3.1 STUDY APPROACH

For the qualitative study, phenomenography was chosen as research approach. This is an approach aimed at describing the qualitatively different ways in which a group of people experience or understand phenomena in the world around them.[129, 130] The word phenomenography originates from the Greek words, *fainemonon* (the apparent, or that which manifest itself) and *grafia* (to describe in words or pictures).[130] The approach was originally developed through empirical studies of learning in higher education in the 1970s and has since been applied within other areas, including medical research.[131-134] Phenomenography aims to take the 'second order of perspective', which is to describe the world as experienced by people, rather than making claims about the world itself. Whilst the more well-known philosophical approach of phenomeno*logy* is focused on the 'essence' or 'life-world' of the participants,[135] the focus of phenomenography is rather on the variation in experiences and the 'every-day life', of the participants.

3.3.2 STUDY PARTICIPANTS

Three main actors of antibiotic use in children were recognized during preparation for the study, namely parents or caretakers, prescribing primary healthcare workers and dispensers or drug-shop owners. The perceptions of antimicrobial resistance among dispensers and drug-shop owners have been previously studied in Tanzania.[116] However, the experiences of the parents/caretakers and primary healthcare workers were largely unknown. Therefore, prescribing primary healthcare workers with different educational backgrounds were included and interviewed individually at their workplace. Parents or caretakers of children under five years of age were further invited to participate in focus group discussions when attending the primary healthcare facilities for the routine care of their children. To achieve variability in participants' educational, social, and economic background, both private and public healthcare facilities were included in Moshi urban and rural district (Table 2). At the facilities participants were recruited by convenience sampling.

3.3.3 DATA COLLECTION

An interview guide (in English) was developed for individual in-depth interviews (IDIs) with healthcare workers and focus group discussions (FGDs) with parents/caretakers. Both were translated into Kiswahili. In total, 20 healthcare workers were included with an equal distribution between males and females (10/10). Most were Clinical Officers (*n*=11), and few were Assistant Medical Officers (*n*=2) who had received three and five years, respectively of clinical training at diploma level, whilst the Medical Doctors (*n*=5) and nurses (*n*=2) had received their training at a university. A detailed description of the participant's background is presented in paper III. Each IDI started with the following question *"Could you please describe your experience of antibiotic prescription in children under 5 years of age?"*.

Parents or caretakers were approached face-to-face and were invited to participate in the study by a local nurse. However, only mothers were present to be included. In total, 54 mothers were included in eight different focus groups the majority of which were carried out in Moshi urban (*n*=6). The general demographics of the participants are shown in paper IV. To ensure trust and confidentiality, the FGDs were performed in a private room. Light refreshments were offered, and the moderator referred only to the initials of each participant during the discussions. The moderator started by asking the participants to identify what an antibiotic is, followed by the main research question *"Could you please describe your experience of antibiotic use in children under 5 years of age?"* with follow up questions. The IDIs and FGD were digitally recorded with one member of the team taking notes as a compliment.

3.3.4 DATA ANALYSIS

All IDIs and FGDs were transcribed verbatim by a member of the team who had been present during the interviews. The transcripts were translated by clinicians at KCMC and parts of the material were back-translated to ensure quality. NVIVO 12 software was used for data management and the steps of analysis were as follows: *familiarization*, *compilation*, *condensation* and *grouping* of answers, followed by *comparison* and *naming* of categories and finally a *contrastive comparison* of categories.[136] The findings were discussed and adapted at regular seminars with the co-authors. The themes and categories that emerged from both the IDIs and FGDs were tested by allowing a neutral

co-examiner to assign uncoded quotations to the final categories. The result showed that agreement was almost unanimous between the authors and the co-examiner.

3.4 ETHICS

The studies were approved by the Kilimanjaro Christian Medical University College Research Ethics and Review Committee in Moshi (No. 661, 809 and 2415) and the National Institute for Medical Research in Dar es Salaam (Vol. IX/2363 and IX/3106). The Regional and District Medical Officers were informed of the studies and gave their permission to visit the study facilities appointed each year. The Regional Ethics Committee in Gothenburg (413-15) gave permission for the molecular methods to be performed in Sweden. Informed oral and written consents were obtained from the children's accompanying parent/guardian in the quantitative study and from healthcare workers or parents/guardians participating in the qualitative studies. The possible power imbalance of Western, female researchers being part of the data collection was taken into consideration. This was counteracted by the local researchers taking the leading role in recruitment of participants, communicating and performing all the interviews in the participants' native language, Kiswahili.

4 RESULTS

4.1 DETECTION AND ANTIBIOTIC SUSCEPTIBILITY OF *S. PNEUMONIAE*

Detection of pneumococci in the nasopharyngeal samples obtained from the children was determined by culture in Moshi (paper I) and by molecular based methods (PCR) in Gothenburg (paper II). The carriage rate of *S. pneumoniae* determined by culture was 31 % (244/775) whilst the molecular-based method could detect pneumococcal DNA in 79 % (614/775) of the children. There was a negative association between culture positivity and Ct value of pneumococci (OR 0.86, 95 % CI 0.83-0.89; *p*-value <0.001), indicating higher likelihood of growth in culture if abundant pneumococci (lower Ct value) were present in the nasopharynx.

Table 3. Antibiotic susceptibility of the pneumococcal isolates (n=244[a]) according to EUCAST 2023[b].

Antimicrobial agent	Susceptible; standard dosing regime *n* (%)	Susceptible; with increased exposure[c] *n* (%)	Resistant *n* (%)
Phenoxymethylpenicillin	132 (54)	-	112 (46)
Benzylpenicillin	142 (59)	98 (41)	0 (0)
Ampicillin	232 (97)	5 (2)	3 (1)
Ceftriaxone	231 (96)	9 (4)	0 (0)
TMP-SMX[d]	25 (10)	16 (7)	203 (83)
Tetracycline	171 (70)	-	73 (30)
Erythromycin	207 (85)	15 (6)	21 (9)
Clindamycin	227 (94)	-	14 (6)
Norfloxacin	244 (100)	-	0 (0)

[a]The number of isolates tested for benzylpenicillin, ampicillin and ceftriaxone were 240, erythromycin 243 and clindamycin 241.

[b]Compared with EUCAST 2018 (paper I) breakpoints for ampicillin, ceftriaxone, TPM-SMX, tetracycline and norfloxacin have been adjusted. The previous term 'Intermediate' has been redefined 'Susceptible with increased exposure' (by for example adjusting the dosing regimen) and 'non-susceptible' now only refer to resistant isolates.[137]

[c]For non-meningitis treatment.

[d]Trimethoprim-sulfamethoxazole.

Antibiotic susceptibility of common antibiotics, used to treat pneumococcal infections in children, was performed in Moshi on viable pneumococcal

isolates (paper I). Few pneumococcal isolates were resistant to ampicillin (3/244), whilst 97 % (*n*=232) were susceptible, which is equivalent to susceptibility to oral amoxicillin, the first line treatment for childhood pneumonia according to WHO[11] (Table 3). The pneumococcal isolates were highly resistant to trimethoprim-sulfamethoxazole (83 %) and resistance to phenoxymethylpenicillin increased from 35 % in 2013, to 52 % in 2014 and 60 % in 2015. All isolates resistant to phenoxymethylpenicillin were also resistant to benzylpenicillin used for treatment in meningitis, according to the EUCAST.[124, 137]

4.2 SEROTYPE DISTRIBUTION OF *S. PNEUMONIAE*

4.2.1 SEROTYPE DISTRIBUTION IN RELATION TO PCV13

In the nasopharyngeal samples (paper II), one or more serotypes/groups was detected in 355 of 614 samples positive for pneumococci by PCR. Since all PCV13 included serotypes (vaccine-types, VTs) could be detected by the PCR method, the 259 samples containing pneumococci in which no serotype could be identified were considered non-vaccine-type (NVT) pneumococci in the analysis.

Prevalence of VTs decreased from 40 % in 2013 to 21 % in 2015 (p-value <0.0001). Meanwhile, prevalence of NVTs increased from 54 % to 63 % (p-value 0.042). Children with partial or full PCV13 vaccination were significantly less likely to be positive for a VT pneumococcus than children without any pneumococcal vaccination.

Changes in serotype prevalence were assessed in paper II. Among the VTs, 6ABCD, 19F, 14 and 19A were the most the common in 2013. Between 2013 and 2015, 6ABCD, 19F and 19A decreased significantly. The NVT 15BC, however, increased in prevalence between 2013 and 2015.

4.2.2 SEROTYPE DISTRIBUTION IN RELATION TO RESISTANCE TO PHENOXYMETHYLPENICILLIN

Among the non-viable pneumococcal isolates (n=241) (paper I), 83 were determined as a VT and 96 as a NVT out of which 11 isolates were found to be non-typeable. In 7 isolates more than one serotype/group were identified. Furthermore, for 30 isolates no serotype/group could not be identified and in 25 isolates the bacterial DNA had been degraded.

In total, resistance to phenoxymethylpenicillin was 51 % (42/83) among VTs with a non-significant change between the years (Figure 6). Resistance to phenoxymethylpenicillin increased significantly among the NVTs from 25 % (7/28) in 2013 to 43 % (12/28) in 2014 and 63 % (25/40) in 2015. Almost all of the NVT 19B isolates were resistant to phenoxymethylpenicillin (12/13 isolates) while the majority of the NVT 15BC isolates were susceptible (15/21

isolates). In 2015, 19B constituted one third (9/25) of the phenoxymethylpenicillin resistant isolates. Among the non-identified isolates and those with degraded DNA, resistance to phenoxymethylpenicillin was 30 % (9/30) and 40 % (10/25), respectively.

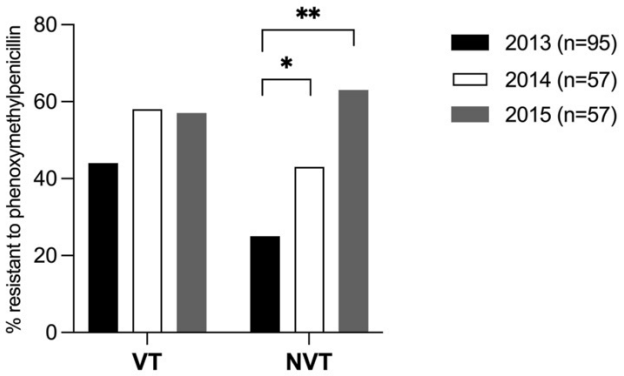


*Figure 6. Percentage of pneumococcal isolates resistant to phenoxymethylpenicillin according to the EUCAST in 2022, in relation to year and PCV13 vaccine-type (VT) and non-vaccine-type (NVT). *p-value 0.029 **p-value 0.0031*

4.3 DETECTION OF PNEUMOCOCCI AND OTHER RESPIRATORY PATHOGENS IN RELATION TO RISK FACTORS, CO-OCCURRENCE AND PARENT-REPORTED SYMPTOMS

Detection of pneumococci, both by culture and PCR, was more common in children closer to 2 years of age and with current symptoms of respiratory infection, than younger children or those without symptoms, as shown by multivariable analysis (Table 4) (paper I and II). Furthermore, detection of pneumococci by PCR was more common in children with a history of gastrointestinal disease and a greater number of siblings, whilst recent antibiotic use decreased the likelihood of being positive for pneumococci.

Detection and co-occurrence of other potential respiratory pathogens were common in the children (paper II). *H. influenzae* was frequently co-occurring with pneumococci and presence of *H. influenzae* was associated with a higher pneumococcal load. About half of the children were positive for rhinovirus/enterovirus, of which the large majority were expected to be rhinovirus,[22] and presence of rhinovirus/enterovirus was also associated with a higher pneumococcal load. On the contrary, adenovirus was less frequently co-occurring with pneumococci and presence of adenovirus was associated with lower load of pneumococci. RSV was only detected during the warm/long rainy season (2014, n=2 and 2015, n=27) and showed no significant correlation to detection of pneumococci.

By multivariable analysis, RSV and adenovirus were shown to be associated to parent-reported fever, rapid or difficult breathing and antibiotic use in the past week (paper II). Parent-reported fever was also associated to detection of parainfluenza virus. *H. influenzae* and all viruses, except for adenovirus were associated to runny nose. Parent-reported cough was further associated to parainfluenza virus, coronavirus and RSV but also to detection of *S. pneumoniae*.

Table 4. Detection of S. pneumoniae by culture and PCR in relation to risk factors. (Landscape format, p. 32)

Table 4. Detection of S. pneumoniae by culture and PCR in relation to risk factors
Total number of children: 775. Pneumococcal detection by culture 31 % (244) vs. by PCR 79 % (614)

	Pneumococcal detection by culture			Pneumococcal detection by PCR		
	No. positive/ Total No. (%)	Univariable analysis; OR (CI 95%), *p*-Value	Multivariable analysis[a]; OR (CI 95%), *p*-Value	No. positive/ Total No. (%)	Univariable analysis; OR (CI 95%), *p*-Value	Multivariable analysis[a]; OR (CI 95%), *p*-Value
Age (close to 2 years)[b]		1.04 (1.01-1.07), 0.004	**1.04 (1.01-1.07), 0.008**		1.11 (1.07-1.15), <0.001	**1.10 (1.06-1.14), <0.001**
Sex, girl	128/374 (34)	*NS*	*NS*	305/374 (82)	*NS*	*NS*
Current symptoms of RTI[c]	146/411 (36)	1.50 (1.10-2.03), 0.010	**1.50 (1.09-2.08), 0.014**	339/411 (82)	1.52 (1.08-2.16), 0.018	**1.50 (1.03-2.19), 0.036**
Presumed pneumonia[d], last 3 months	25/90 (28)	*NS*	*NS*	67/90 (74)	*NS*	*NS*
History of gastrointestinal disease	68/191 (36)	*NS*	*NS*	170/191 (89)	2.55 (1.56-4.17), <0.001	**1.84 (1.09-3.11), 0.022**
Underweight[e]	10/31 (32)	*NS*	*NS*	25/31 (81)	*NS*	*NS*
Stunted[f]	79/236 (33)	*NS*	*NS*	181/236 (77)	*NS*	*NS*
Antibiotic use in the child, last 7 days	40/150 (27)	*NS*	*NS*	112/150 (75)	*NS*	**0.55 (0.34-0.89), 0.014**
Mother's education, ≤7 years	168/493 (34)	1.40 (1.02-1.93), 0.040	*NS*	410/493 (83)	1.89 (1.33-2.69), <0.001	*NS*
Father's education, ≤7 years	142/411 (35)	1.37 (1.01-1.87), 0.044	*NS*	341/411 (83)	1.67 (1.17-2.37), 0.004	*NS*
Adult smoking in the household	38/114 (33)	*NS*	*NS*	87/114 (76)	*NS*	*NS*
Solid fuel[g] used for cooking	216/658 (33)	*NS*	*NS*	523/658 (79)	*NS*	*NS*
Number of siblings[b]		1.14 (1.01-1.29), 0.031	*NS*		1.22 (1.04-1.43), 0.012	**1.20 (1.01-1.42), 0.043**
Crowding[b, h]		1.18 (1.03-1.34), 0.015	*NS*		1.19 (1.01-1.40), 0.033	*NS*

[a]Adjusted according to year of sampling and covariates included in the univariable analysis
[b]Continuous variables (all other variables are categorical)
[c]Respiratory tract infection (cough, runny nose, fast or laboured breathing with or without fever)
[d]Respiratory tract infection with rapid or laboured breathing (according to parent/guardian)
[e]Weight in relation to age <-2SD
[f]Height in relation to age <-2SD
[g]Firewood or charcoal
[h]No. of people per room in household

4.4 ANTIBIOTIC PRESCRIPTION AND USE IN TANZANIAN CHILDREN

Antibiotic use among the children included in the quantitative study (paper I) was high; 54 % had been treated with antibiotics in the past 3 months according to the parent/guardian or as documented in the child's medical log (Table 5). Number of treatments/child in the past 3 months was higher in 2015 (216/213=1.01) compared to 2014 (155/224=0.69) and 2013 (241/338=0.71). Of the antibiotics used in the past week, the majority were reported to be 'prescribed' although it was not clarified whether the antibiotics were prescribed by a healthcare worker or a pharmacist. The most common antibiotics were amoxicillin/ampicillin, followed by trimethoprim-sulfamethoxazole and erythromycin. In many cases (13 %), the parent did not recall the name of the antibiotic, nor could it be retrieved from the medical log.

Table 5. Parent-reported use of antibiotics in children under 2 years of age, 2013-2015 (n=775)[a].

	n (%)
Antibiotic use in the previous;	
<7 days	150 (19)
Prescribed	131 (87)
Over the counter	19 (13)
>1-4 weeks	188 (24)
>4-12 weeks	215 (28)
Type of antibiotic used in the past 12 weeks, *n*=612	
Amoxicillin/ampicillin	289 (47)
Trimethoprim-sulfamethoxazole	102 (17)
Erythromycin	58 (9)
Cloxacillin	21 (3)
Gentamycin	21 (3)
Metronidazole	14 (2)
Phenoxymethylpenicillin	5 (0.8)
Benzylpenicillin	5 (0.8)
Chloramphenicol	5 (0.8)
Other	13 (2)
Unknown	79 (13)

[a] Based on structured interviews and review of the child's medical log if available.

Notably, erythromycin, belonging to the macrolides, is considered a 'watch' group antibiotic due to its higher resistance potential, whilst all other antibiotics listed in Table 5 are considered key access antibiotics.[104] In total,

77 % of the antibiotics used in the children belonged to the ‘access’ group, 10 % to the ‘watch’ group (erythromycin or azithromycin) whilst no antibiotic was found to belong to the ‘reserve’ group (last resort antibiotics).

The qualitative studies (paper III and IV) further explored the experiences of primary healthcare workers and mothers, aimed at understanding *why* there was such a seemingly high use of antibiotics in children residing in Moshi. Examples of citations from the participants, connected to the themes that emerged during analysis of the IDIs with healthcare workers and FGDs with mothers, respectively, are shown in Table 6.

In summary, the healthcare workers relied mainly on the physical examination of the child and the history from the mother when deciding whether they would prescribe an antibiotic. They used different strategies when dealing with uncertain cases of childhood infections, mainly dependant on their self-confidence in advising the mothers on non-antibiotic treatment which was often seen as a time- and energy-consuming task. Some healthcare workers in public facilities experienced limitations hindering their choice of which antibiotic to prescribe owing to insufficient supplies. Whereas others were suspicious about some of the antibiotics which were indeed available, being of poor quality. The majority agreed that prescription of antibiotics by pharmacists led to irrational antibiotic use in children. Antimicrobial resistance was partially acknowledged by the healthcare workers, although this was mostly seen as a problem for the individual misusing antibiotics but was less commonly seen as a public health emergency.

The mothers had different conceptions of the causes of childhood disease, often relating disease to the natural environment of the child such as cold, dust etc. Antibiotics were often seen as a remedy for common symptoms or a universal treatment for common childhood diseases, but few were aware of antibiotics as a treatment for bacterial disease. Whilst some mothers expressed that they would be disappointed if not prescribed an antibiotic when attending a healthcare facility, it became apparent through the discussions that their greatest wish was for the sick child to be properly assessed and to receive advice from the healthcare worker. Some mothers were hesitant in asking questions of the healthcare workers out of fear of being rebuked, owing to previous experience of disrespectful consultations.

Table 6. Themes that emerged in the phenomenographic analysis of interviews with prescribing primary healthcare workers (paper III) and mothers (paper IV) regarding their experiences of antibiotic prescription or use of antibiotics in children under five years of age.

Theme		Citation (example)
Prescribing primary healthcare workers		
1.	Conceptions in relation to the prescriber	*"Previously we used to give medicine to children without investigations. But after I went for further studies, I realized that not all children are to be given antibiotics." (HW 15)*
2.	Conceptions in relation to the mother and child	*"(…) when a low-income family comes to the health facility (hospitali) there are charges like consultation fee, laboratory investigations fee. So, they skip that and go to the pharmacies and explain what is their problem and they buy [antibiotics]." (HW 8)*
3.	Conceptions in relation to other healthcare actors	*"Another major problem that can cause antibiotic resistance is limited antibiotic stock. We need an adequate stock in our facility." (HW 6)*
4.	Conceptions in relation to outcome	*"This [treatment failure] happens in relation to [work] resources (…) As a doctor one has to fight in all ways possible to do the job because there are times drugs become resistant or there is a misdiagnosis and you have to look for an alternative or make a referral if the patient doesn't get well; they will be required to go to a higher-level hospital; you cannot do everything right." (HW 16)*
Mothers of children under-five		
1.	Conceptions of disease and antibiotics	*"There are many types of kikohozi (coughs), the one for kifua kikuu (pulmonary tuberculosis) and the kikohozi cha kawaida (normal cough). The kawaida (normal) is the one we use antibiotics."* (FGD 7)
2.	Conceptions of accessing treatment	*"(…) they say that treatment for children less than five years is free (…) it is true that the consultation is free, but then the daktari (doctor) tells you we do not have this dawa (medicine), go and buy in the duka la dawa (pharmacy) (…) you have to go and ask for money from the man and he tells you 'I don't have money, take this bus fare, go and get the child treated'. You tell [him] but he insists that treatment is free for children."* (FGD 3)
3.	Conceptions of administering medication	*"To be honest I [personally] do not ask questions. The daktari (doctor) writes the prescription, [but] I don't know how to read… Someone else when you ask him [the doctor] gets angry. Mostly amoxicillin is the one I can read [identify], even the day my child was given 25 injections I did not ask."* (FGD 8)

Both the healthcare workers and the mothers acknowledged the effect of low socioeconomic status on healthcare seeking and antibiotic use. According to the mothers, they preferred healthcare facilities as a primary place to seek medical attention for their child (Figure 7). However, when faced with financial constraints or if the child fell ill at night, they were often forced to primarily attend pharmacies with their child due to the proximity of these and to avoid barriers or unforeseen costs related to attending the public healthcare facilities. These barriers or costs included travel, long waits leading to loss of possible income, dubious costs for registration and purchase of prescribed medicine at pharmacies. However, it was not always an absolute deficit, rather restricted access to household money and lack of support from their husbands that led them to primarily attend a pharmacy with their sick child. Some mothers primarily sought the advice of a trusted neighbour if their child fell ill to receive advice regarding treatment or when to seek healthcare. However, if the child did not improve with or without treatment, they agreed that healthcare facilities were trustworthy, and they would bring the child there.

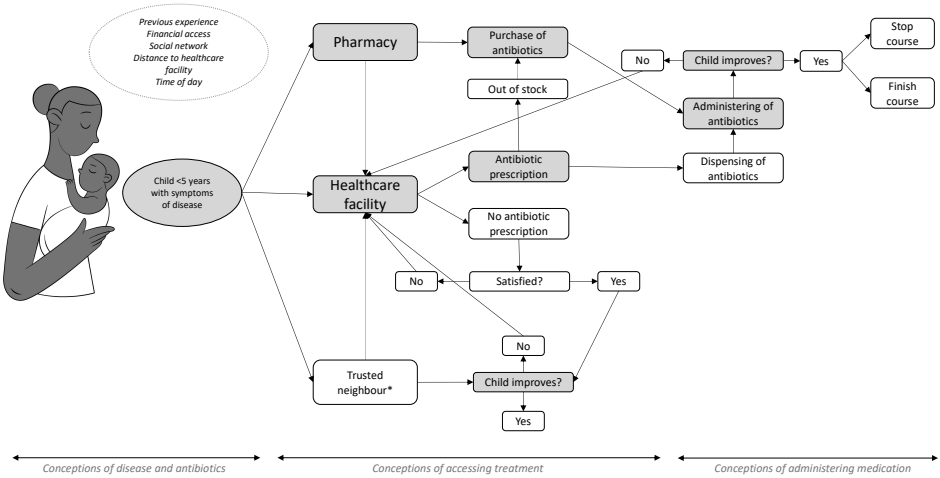


Figure 7. Model of healthcare seeking behaviour for children under five years in relation to antibiotics; based on focus group discussions with mothers residing in urban and rural Moshi, Tanzania during 2019.

5 DISCUSSION

This thesis has, through qualitative and qualitative studies, described use of antibiotics and presence of respiratory pathogens with focus on *S. pneumoniae* in Tanzanian children after introduction of the PCV13. Drawing upon on these results, some aspects of antimicrobial resistance and antibiotic use will be discussed, along with possible ways of improving antibiotic stewardship and care of Tanzanian children with respiratory or pneumococcal disease.

5.1 ANTIBIOTIC SUSCEPTIBILITY IN PNEUMOCOCCI, ANTIBIOTIC USE IN TANZANIAN CHILDREN AND PROJECTED IMPACT OF THE PCV13

To date, determination of antibiotic susceptibility in pneumococci can only be carried out by culture in routine diagnostics, a time- and resource-demanding method which is not common practice in routine healthcare in sub-Saharan Africa. High resistance to trimethoprim-sulfamethoxazole, as shown in paper I was, however, not unexpected. This cheap antibiotic was previously considered first-line treatment for childhood pneumonia,[138] it was still the second most used antibiotic in the children as shown in this thesis and is recommended as a prophylaxis in HIV-exposed infants and HIV-positive individuals.[11] Amoxicillin is nowadays considered first line-treatment for childhood pneumonia and, according to our data, it is still expected to be effective in Tanzania. Amoxicillin was widely used in the children, according to a healthcare worker (paper III) due to its availability and recommendations by treatment guidelines. Furthermore, an increase in resistance to phenoxymethylpenicillin was noticed among the isolated pneumococci, although use of this antibiotic was rare. In consequence, use of benzylpenicillin for pneumococcal meningitis may be a less reliable option in Northern Tanzania. If benzylpenicillin is used for severe pneumonia, higher doses (100 mg/kg 4 times per day[139]) may need to be administered than what is suggested in current WHO guidelines for paediatric hospital care.[140] Erythromycin was the third most common antibiotic used in the children, and 9 % of the pneumococcal isolates were resistant to this antibiotic which is in line with previous studies in sub-Saharan Africa but lower than global estimates.[141] The widespread use of erythromycin is of concern though, since the macrolides (including erythromycin) has a high potential to drive antimicrobial resistance in pneumococci.[89, 142] In contrast, a recent study of pneumococci isolated from children under 2 years of age in eastern parts of the Democratic Republic of Congo, showed resistance to phenoxymethylpenicillin and erythromycin as high as 80 % and 40 %, respectively.[143] This reflects the importance of providing local surveillance as resistance may vary greatly.

Use of antibiotic in children in our study was indeed high. Over 50 % had been treated with antibiotics in the past three months. However, this was an estimate

based mainly on parental recall which may under-estimate the true use of antibiotics.[144-146] Based on data on antibiotic prescription in children from multiple sources, including observations of sick-child visits at health-care providers, Fink *et. al.* (2020)[100] suggest Tanzanian children are on average exposed to 20 courses of antibiotics before the age of five. This indicates that the true antibiotic use in Tanzanian children may be even higher than is reported here. Not surprisingly, detection of respiratory syncytial virus (RSV), the most common aetiology of pneumonia and bronchiolitis in children,[23] was associated to antibiotic use in paper II. Therefore, higher use of antibiotics as observed in 2015, compared to previous years, may be related the observed, concurrent epidemic of RSV.

Use of pneumococcal conjugate vaccines in children is an important way of preventing severe pneumococcal disease in children.[59] In paper II we observed a 50 % decrease in prevalence of vaccine-type (VT) pneumococci detected in nasopharynx of children under two years between 2013 and 2015. Further, children with partial or full PCV13 immunization were less frequently positive for a VT pneumococcus. This indicates that the PCV13 will have a substantial impact on childhood mortality due to pneumococcal pneumonia and IPD in Tanzania.[78-80, 147, 148] However, VTs were still detected in 21 % of the children in 2015, including serotypes with high probability of causing invasive disease, such as 14 and 9V.[66] The emerging non-vaccine-types (NVTs), such as 15BC are, in general associated to lower probability of causing severe disease in children but are globally contributing to a larger share of IPD cases after PCV introduction.[149, 150] High remaining VT pneumococci in children after PCV introduction has been shown in other sub-Saharan countries,[151-154] thus hampering indirect effects of the vaccine. This has led to an evaluation of the 3+0 versus 2+1 schedules, currently being carried out in Malawi[155] to ascertain whether a change to the 2+1 schedule in high burden settings may improve herd immunity.

In the post PCV13 era, pneumococci are exposed to selective pressure from both antibiotics and the vaccine, favouring resistant NVT strains.[156] In fact, the above-mentioned increase in resistance to phenoxymethylpenicillin between 2013 and 2015 was largely driven by NVT pneumococci. Moreover, large clonal analysis of pneumococci showed that a small number of clones often predominate in the antimicrobial resistant population[71] and the increase in resistant NVTs following vaccine introduction was mainly due to the

expansion of existing clones.[156] Consequently, the sharp increase of the NVT 19B resistant to phenoxymethylpenicillin, indicates a clonal spread following PCV13 introduction, although analyses to confirm this were not performed in these studies.

The performing of serotyping and antibiotic susceptibility tests on pneumococci detected in the general child population is a feasible way of monitoring effects of PCV introduction and the efficacy of recommended treatment for pneumococcal disease. However, considering that some serotypes are more common in carriage than disease, these results cannot be directly projected onto changes in serotypes causing severe or invasive disease in Tanzanian children.[66] Nevertheless, in countries such as The Gambia[78, 147] and Malawi[79, 148] where both nasopharyngeal carriage of pneumococci and invasive disease have been monitored, similar reductions in nasopharyngeal carriage have led to significant reductions in severe pneumococcal disease. Furthermore, pneumococcal serotypes carried during longer periods in the nasopharynx may more often be exposed to the selective pressure of antibiotics.[156] Thus, the resistance found in the carried pneumococci may be slightly higher than on average in serotypes with higher disease potential.

Although the children in our quantitative study were mainly attending the healthcare facility for vaccination or growth monitoring with only a minority attending for an illness, detection of multiple respiratory pathogens in the nasopharynx was common. In line with previous studies, co-occurrence of pneumococci and *H. influenzae* in nasopharynx were shown across the analyses.[157, 158] Pneumococci and non-typeable *H. influenzae* are known to form biofilms, shown to be involved in acute and longstanding *otitis media*.[159, 160] We were also able to show an increase in pneumococcal load in presence of rhinovirus/enterovirus, which may be due to indirect effects of inflammation leading to increased adhesion of pneumococci to epithelial cells.[53] The way in which different virus and bacteria interact in the nasopharynx and contribute to the spread or development of disease is only beginning to be elucidated.[36] The production of local inflammatory factors and upregulated epithelial receptors, as occurs during viral infections, is however an event known to be a prerequisite for conversion of pneumococcal carriage to invasive disease.[53] Similarly, childhood pneumonia is increasingly described as a multi-pathogen disease which needs to be addressed in future studies exploring the aetiology of childhood pneumonia in the era of conjugate vaccines.[23]

5.2 THE NEED OF SURVEILLANCE AND LEGAL INFRASTRUCTURE IN RELATION TO ANTIBIOTICS IN TANZANIA

Legislation and availability of antibiotics in a country or region are a major determinant of use at a macro level.[161] In Tanzania, legislation prohibits sale of non-prescribed antibiotics, but enforcement is lacking.[113] Our study confirms ADDOs or *'duka la dawa'* as an integral part of the healthcare system, in general trusted and appreciated by the mothers for their close accessibility, as well as their prompt and cheap service. However, market forces combined with lack of punishment for not adhering to regulations, have clearly led to an inappropriate dispensing of antibiotics both in urban and rural areas of Tanzania.[113, 114, 118] In other words, market driven sales of antibiotics are not compatible with rational antibiotic use, thus a strengthening of legal infrastructure is necessary. It should be noted that our studies mainly reflect the use of antibiotics in children in urban areas, although our qualitative study also included rural study sites. Future studies are warranted to investigate availability of antibiotics and healthcare seeking behaviour for children under five years in rural parts of Tanzania where healthcare facilities are less accessible.

In recent years there have been large investments aimed establishing a national antimicrobial resistance surveillance system in Tanzania, with data being shared in the WHO Global Antimicrobial Resistance Surveillance System (GLASS).[84] This is encouraging as surveillance of antimicrobial resistance and antibiotic prescription, sale and consumption, are vital to ensure accountability in the fight against antimicrobial resistance. Moreover, surveillance of the quality of available antibiotics is also important since there are evidence that sub-standard or falsified medicines are increasing worldwide.[162] This disproportionally affects low- and middle-income countries, resulting in huge economic losses and unnecessary deaths.[163, 164] The quality of available antibiotics was a concern for some healthcare workers in our qualitative study (paper III). Although their experience of treatment failure may, in some cases be attributable to other factors, it was clear that they had a diminished level of trust in the industry and national health ministries and were calling for better regulations.

The selective pressure induced by use of antimicrobials is key in the development of antimicrobial resistance.[142] But the spread of resistance genes and resistant strains in the environment may have an even greater impact, resulting in increased prevalence of antimicrobial resistance. Crowded living conditions and a lack of clean water and sanitation may therefore be among the main reasons why low- and middle-income countries have higher prevalence of antimicrobial resistance compared with high-income countries, irrespective of levels of consumption.[93] Poor governance and a large private healthcare sector have also been associated to higher antimicrobial indices.[93] It is therefore plausible to suggest that improved use will not be sufficient in the fight against antimicrobial resistance. Nevertheless, increasing antibiotic consumption and resistance in Tanzania have not yet reached the prevalence of many southeast Asian countries, indicating that there is an opportunity to intervene. Meanwhile, the notably high burden of deaths associated to bacterial antimicrobial resistance in sub-Saharan Africa are not only caused by increased bacterial resistance, but it is also attributed to limited access to second- and third-line antibiotics.[103] Thus, antibiotic governance in Tanzania also involves improving access to second- and third-line antibiotics in severe infections.

5.3 IMPROVING ANTIBIOTIC STEWARDSHIP AND CARE FOR CHILDREN WITH RESPIRATORY OR PNEUMOCOCCAL DISEASE

Although awareness of antimicrobial resistance was only partly acknowledged by the healthcare workers and largely unknown to the mothers in our studies, raised awareness alone is likely to have a limited impact on antibiotic use.[165-167] Rather, the precarity that affects both the working conditions of healthcare workers, such as limited antibiotic stock, and living conditions of the mothers, including lack of access to transport and household money, needs to be addressed. In line with previous qualitative studies, we recognise (in paper III and IV) that antibiotics have become a compensation for lacks in infrastructure in Tanzania.[168-171] The need for improved surveillance and legal infrastructure in relation to antibiotics has been described above and below, in line with Denyer Willis and Chandler (2019),[169] antibiotics will be discussed further as a compensation for *lack of care, equity, and hygiene*. Understanding these drivers of antibiotic use is vital when shaping interventions to improve antibiotic stewardship.

The focus in the literature has often been on 'patient demand' as a driver of inappropriate antibiotic prescribing. Although this was a concern for some healthcare workers, it became clear in the focus group discussions that the mothers' wish, over and above wanting an antibiotic prescription, was for the child to be properly assessed and to be reassured of the child's recovering. The healthcare workers further viewed the task of providing advice for non-antibiotic treatment as time- and energy-consuming, rendering antibiotics a *compensation for care*.[169] Improved antibiotic stewardship in Tanzanian children thus include a transformation of primary healthcare from the provision, or not, of medicine, to the provision of care. In the focus group discussions, some mothers gave accounts of disrespectful treatment of healthcare workers. In recent years, awareness has been raised of the practice of disrespectful treatment in maternal and newborn care at healthcare facilities, globally[172] and in Tanzania.[173-176] How mothers affected by this may perceive healthcare seeking for their children after experiencing neglect or disrespect during delivery is less known. However, in general the mothers participating in our study still trusted in the care of healthcare facilities. This may, however,

be biased by the fact that the focus group discussions were carried out at the premises of a healthcare facility. Improved care requires the continued professional development of healthcare workers who need support to provide quality care. One way of achieving this may be through the setting up of structures, or networks, providing peer-to-peer continuous education and support as suggested by one of the healthcare workers in our study (paper III).

The concept of 'care' presented here also incorporates improvement of supportive care or treatment needed in young children affected by acute respiratory disease. This includes clearing of airways, nutrition, inhaled bronchodilators, antipyretics, and not least oxygen. While the former may be achieved with relatively few resources, increased availability of oxygen treatment requires larger investments in sub-Saharan Africa but may be achieved through new techniques.[177] Currently, the IMCI[11] includes some advice for supportive treatment, but a greater emphasis on this needs to be given in future updates. To improve the predictive value for pneumonia in primary healthcare, auscultation has been suggested as a tool to be taught at all levels of healthcare.[25] However, adherence to the IMCI has, in practice been poor[13-15] while it is likely that full application including administration of paracetamol for fever, inhaled bronchodilator in cases of wheezing, history of previous similar episodes and correct collection of vital signs, may increase specificity.[178, 179] Furthermore, use of rapid diagnostic tests to help determine need for antibiotics in children may seem promising, but a previous study in Tanzania indicates that this cannot be used as a single tool for treatment decisions.[180] Our interviews with healthcare workers also show that, if rapid-diagnostic tests are not implemented along with sufficient training and free-of-charge, these may change little in terms of prescribing behaviour (paper III).

Antibiotics as a *compensation for inequity*,[169] came across in the qualitative study as children from low-income families more often received inappropriate antibiotic treatment. However, for both healthcare workers and mothers it was clear that, when faced with poverty they tried to achieve the best outcome with the available resources, or absence thereof, at hand. In some cases, antibiotics were also a compensation for gender inequity, as some mothers carrying out domestic work, did not have full access to funds for transport etc., necessary for seeking care at healthcare facilities. The aspect of gender inequality in relation to antimicrobial resistance thus calls for further consideration. Furthermore, the importance of water and sanitation to combat antimicrobial

resistance has gained increased attention as previously discussed.[93] Although enteric diseases may spread directly through contagion in water, respiratory viruses and bacteria spread more frequently in crowded conditions with limited access to clean water for hygiene. Antibiotics for treatment of infectious disease deriving from such circumstances may in part be, *a compensation for lack of hygiene*.[169] Importantly, improved water and hygiene may prevent both all cause respiratory and pneumococcal disease, and the increased prevalence of antimicrobial resistance.

The task of transforming infrastructure, healthcare, and inequalities to combat antimicrobial resistance and improve child health may seem a daunting. One of the main conclusions in paper IV is that a feasible target for intervention in Tanzania may involve an increased presence of community health workers (CHWs) to support women in appropriate healthcare seeking for their sick children. In fact, a pilot project has been carried out in Moshi providing education for CHWs on topics such as antimicrobial resistance and antibiotic use in children.[27] Increased use of mobile phones for CHW and within the healthcare system at large, to direct healthcare seeking or to provide follow-up,[181] is another area of improvement that would not involve large investments given that an estimated 91 % of the population already had access to mobile phones in 2022.[182] Although national efforts have been made to step up the CHW program in Tanzania,[111] the CHWs who had gained training during the first part of the program were largely employed within the primary healthcare system.[27] Thus, renewed efforts need to be undertaken to provide the necessary training, paid employment and supervision needed for Tanzanian CHWs who are indeed serving their communities, for them to be efficient in their endeavours.[109, 110, 183]

6 CONCLUSIONS

The quantitative part of this thesis reveals high use of antibiotics in Tanzanian children and increasing resistance to phenoxymethylpenicillin in pneumococci shortly after introduction of the PCV13. This highlights the need for improved surveillance of antimicrobial resistance and strengthening of legal infrastructure in relation to antibiotics in Tanzania. Although the PCV13 is expected to have a substantial effect on severe pneumococcal disease in Tanzanian children, the high co-occurrence of other potential respiratory pathogens, high remaining prevalence of vaccine-type and emerging non-vaccine-type pneumococci, reveal the limitation of single interventions. To further prevent childhood mortality due to respiratory and pneumococcal disease, investments are needed to improve supportive care at healthcare facilities and water and sanitation in the communities.

Furthermore, the qualitative studies show that improved antibiotic stewardship in Tanzanian children require a focus on *trust* and *support*. Healthcare workers need to trust in the efficacy of recommended antibiotics, and they need support in developing their clinical and consultation skills. The former may be achieved through surveillance of bacterial resistance and quality control of antibiotics, and the latter through continued, peer-to-peer professional education. Mothers should be able to trust in the care provided at healthcare facilities, and they need support as to when to seek medical care for their children. Equity, both in the household and public arena, and a strengthening of networks such as community health workers are necessary in order to achieve this.

7 FUTURE PERSPECTIVES

As a medical student, I completed a short-term internship in Kenya after finishing my second year. Among many things, I experienced the death of an infant due to pneumonia, the introduction of the PCV13, the devastating effects of the more and more frequently occurring droughts and the bargaining over cattle with mobile phones among the nomadic people groups. But not least, I experienced the community of female healthcare workers, vaccinating and prescribing antibiotics for children while drinking numerous cups of tea at the small, mission-funded primary healthcare clinic where I was based. Later, in 2013, I attended a global health conference where the late Hans Rosling opted for a focus on improved health in the poorest populations, all while remembering that most of the world's population now live in middle-income countries. At the same conference, Johan Rockström presented the case for focusing on the effects of climate change on human health worldwide, to create an incentive for action among the general population.

Today, the world faces multiple challenges to ensure a future for the world's children.[184] Increased antimicrobial resistance is one of these, challenging our perceptions of the capability of modern medicine. Meanwhile, climate change and loss of biodiversity challenge the very foundations of life on earth.[185] The burden of these disruptions disproportionally affects the poorest populations and the children, who have done the least to contribute to CO_2 emissions.[184] Paradoxically, exploitation of finite natural resources has until now served as the very tools with which development, and thereby improvements in human health, have been built.[186]

Science tells us that health and well-being for all at all stages of life, as is the aim of the Sustainable Development Goal 3, will not be achieved within the current paradigm driven by profit and fossil fuels. Health for all requires a completely new way of living together, not only as humans, but humans together with the animals, microbes, plants, and water on which we all depend.[187] To achieve this, our primary shortfall is not knowledge, rather dreams and, not least courage. Meanwhile, researchers are needed as watchmen, overseeing an ever-changing world to create the bigger picture needed in order to direct human efforts to where it is most needed.

At last, the urgency of the current multiple challenges means we may even need to take steps towards fulfilling the dream of a new way of living, without completely envisioning it.[188] To achieve this, as concluded for antibiotic stewardship, daring to make the necessary changes requires *trust* and *support*. In the face of the erosion of social cohesion, this in turn requires strengthening of societal networks, or in other words: fellowship and dreaming over numerous cups of tea.

Let's begin.

Figure 8. Women in front of Mount Kilimanjaro. (Published with permission, Johan Franzén, photographer.)

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