Preventing and controlling infectious disease outbreaks and AMR: From counting cases to monitoring risks

Preventie en bestrijding van infectieziekte-uitbraken en antibioticaresistentie: van ziektegevallen tellen naar risico monitoring
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 31 maart 2023 des middags te 2.15 uur

door

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geboren op 17 november 1985
te Roeselare, België

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The degree is awarded as part of a Joint Doctorate with Instituut voor Tropische Geneeskunde, Antwerp, Belgium.

Dit proefschrift werd mede mogelijk gemaakt met financiële steun van Fonds Baillet Latour.

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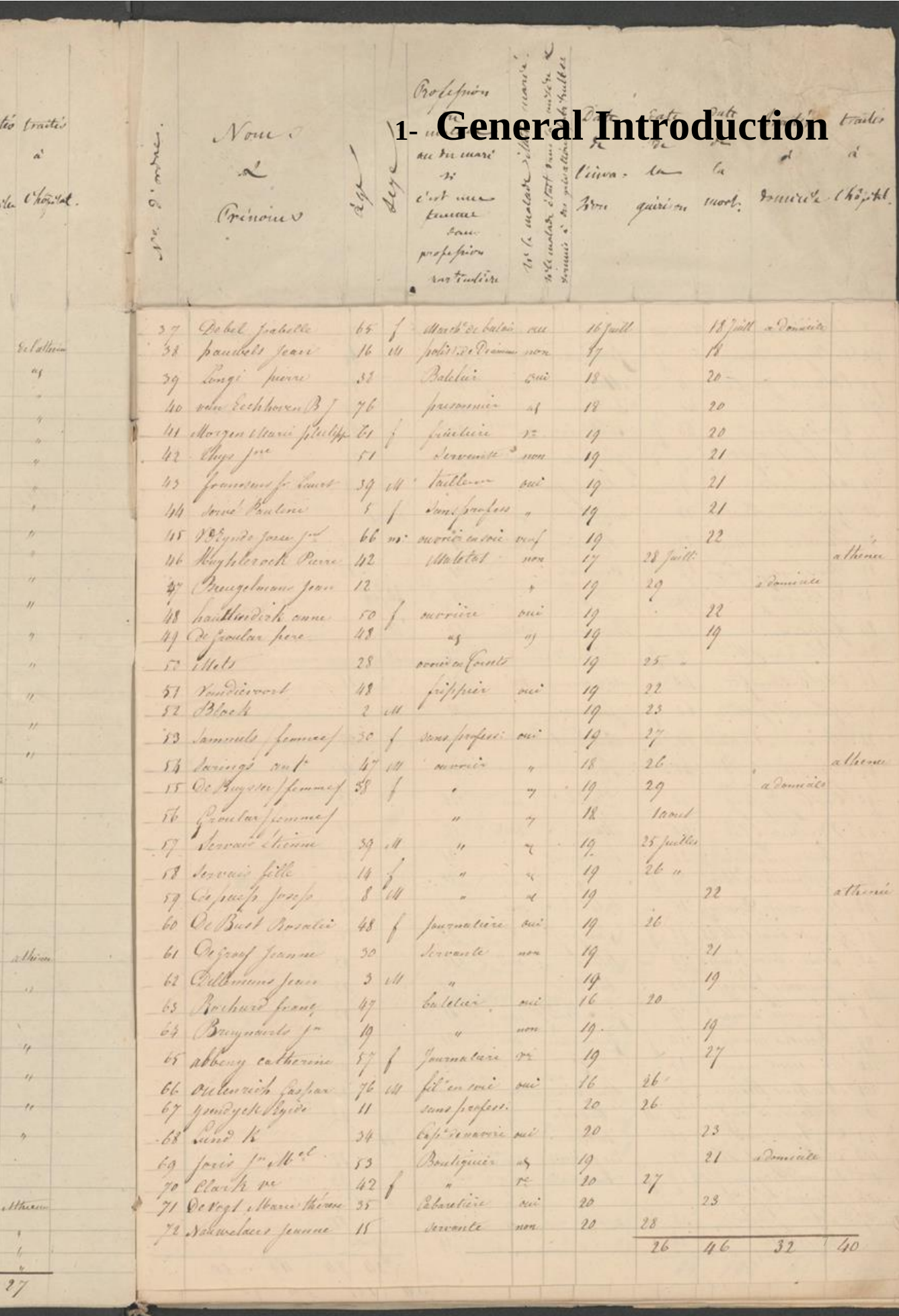
Page 6-7: Extract from « Etat indicatif des personnes qui ont été atteintes du Cholera-Morbus dans la ville d'Anvers pendant l'année 1832 », scan from Stadsarchief Antwerpen.

1- General Introduction



Contemporary determinants of the spread of infectious agents

Despite a more-than-thirty-year decline in the global burden of infectious diseases (1), the frequency of infectious disease outbreaks, the size of outbreaks following animal-to-human spill-over events, and the proportion of outbreaks of antimicrobial-resistant (AMR) pathogens have all been increasing (2–4). Increased mobility, travel, urban populations and population densities, agricultural expansion, deforestation, large scale meat production, wildlife trade, and climate change are contemporary determinants of the emergence and spread of infectious agents, and are most outspoken in developing countries (4–8). Urbanisation is fastest in Africa and Asia, with low-income countries reaching 50% urban populations by 2050 (9). Each week, through migration urban populations in Asia grow by 0.88 million, in Africa by 0.23 million, out of 1.2 million globally (5). Higher temperatures facilitate the presence of vectors such as Anopheles and Aedes aegypti and albopictus mosquitoes, sand-, blackflies, aquatic snails, and ticks (10,11), resulting in more vector-borne disease outbreaks (3).

These determinants were pivotal in the emergence and transmission of infectious agents during most large international outbreaks in the past decade: SARS-CoV-2; several Ebola Virus Disease outbreaks, previously rare and limited to remote places, now frequent spill over from an animal reservoir in intensely mobile and dense populations, spreading to large cities in West-Africa (2013-16), Eastern DR Congo (2018-20), and Uganda (2022); similarly, when Zika virus spread from islands in the Pacific to Brazil, on the course of a few months it reached nearly all countries in the Americas and South Asia (2015-16); Yellow Fever spread to urban areas in Angola, then reaching cities in DR Congo when many migrant workers returned from Angola (2016); the large outbreak of extensively drug resistant (XDR) typhoid fever in Pakistan (2016-2020) as a result of problems with sewage systems in areas densely populated with poor city dwellers; mpox virus could reach most industrialised countries within weeks, spread widely within a globally connected population of men having sex with men.

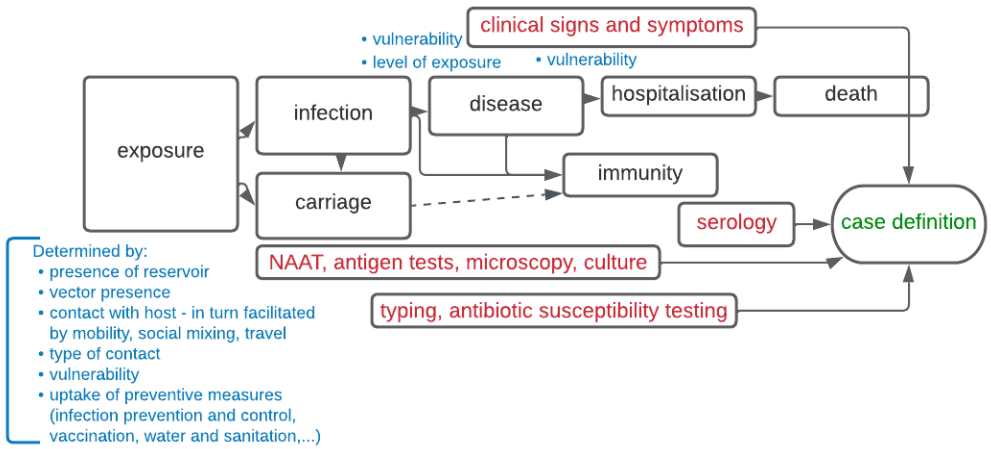


Figure. Schematic overview of the natural history of disease and corresponding determinants and diagnostic components

Surveillance systems designed to timely inform the prevention or control of infectious diseases

Infectious disease control measures have been, especially in low- and middle income countries (LMIC), largely based on healthcare facility-based reporting of different stages of disease progression: laboratory-confirmed infections, clinical disease, hospitalisations, or deaths (Figure). Facility-based case reports are generally readily available and interpretable, using standardised formats, though delayed by disease progression from infection to disease, healthcare seeking, diagnosis, and reporting. In low-resource settings, patients often self-medicate, delay healthcare

seeking or seek care at private or informal providers (12). Additionally, primary healthcare facilities commonly lack diagnostic capacity to confirm cases (13), and case data cannot usually be linked to other clinical or demographic data – complicating the identification of populations at increased risk or estimating measures of disease frequency. When an outbreak is eventually detected, the window for early outbreak containment has in some cases passed.

Whether public health surveillance is needed, what type of surveillance system is needed, what case definitions, whether laboratory capacity is needed, and what data will be collected will depend on the disease control strategy, on available resources, and on acceptability of control measures or of surveillance. The objective of a surveillance system can be to alert on potential new outbreaks, to characterise patterns of disease (e.g. monitor disease trends, to determine (risk factors for) susceptibility to infection (e.g. through sero-surveillance), health status (e.g., fatalities, long-term sequellae)), to monitor the risk of outbreaks (e.g., presence of a vector, evolution of infectious agents), or to assess the effectiveness or uptake of a control intervention (Table). To detect or count disease, infections or other events, well-specified case definitions are indispensable. These can be clinical, laboratory-based, epidemiological (e.g. physical contact with another case), or based on combined criteria.

Table. Strategies of infectious disease control and matching surveillance objectives and systems

Control strategy	**Example**	**Surveillance system**	**Surveillance objective**	**Control measures**
Reduce burden of disease	Childhood diarrhoea Cholera Influenza Covid19	Facility case reports Sentinel case reports Social mixing studies	Detect case count increases Detect outbreaks Quantify/monitor number of contacts	Zinc supplementation; Oral cholera/ Influenza / Covid19 vaccination; WASH; Physical distancing
Interrupt transmission	Tuberculosis Plague Measles Yellow Fever Polio	Mandatory case reporting Contact tracing Rodent surveillance Vector surveillance Sewage	Detect new cases and clusters Detect outbreaks Measure risk	Contact tracing, testing and treatment; Screening risk groups; Use of masks; Ventilation; Vaccination
Eliminate infectious agent: reservoir or source	Ebola Foodborne infections (STEC, Salmonella, Listeria)	Treatment facility case report Contact tracing Hospital laboratory surveillance (with typing of clusters) Syndromic surveillance (Hemolytic uremic syndrome) in pediatric wards Food chain inspection	Detect new cases and clusters Evaluate control performance	Early detection and isolation Recall contaminated food, close food production plants
	Hospital acquired MRSA, C. difficile, carbapenemase-producing Enterobacterales, vancomycin-resistant Enterococcus faecium	Hospital microbiology complemented by environmental sampling	Detect clusters of cases; Identify source	Isolation of cases; disinfect environment
Prevent spread to humans	Anthrax Plague	Animal mortality surveillance	Detect new cases and clusters Monitor the risk of spread to humans	Vaccine, health education Rodent control
Ensure intervention s' effectiveness	Antimicrobial resistance	Antibiotic sales Antibiotic use from patient exit surveys Hospital AMR outbreak investigations	Measure antibiotic use, a risk factor for increasing AMR prevalence	Guide antibiotic use

STEC, Shiga Toxin-like E. coli, MRSA, methicillin-resistant *Staphylococcus aureus*, AMR, antimicrobial resistance

Public health measures can be triggered by a single case or by a detected cluster of cases (e.g., genomic or antimicrobial susceptibility profile similarity). Furthermore, signal thresholds can

trigger action, e.g. an increase in case incidence compared to baseline or to previous years, by time, place or person. An indication of new introductions or of a change in characteristic of the infectious agent can also require action, e.g., carbapenem resistance detected among Enterobacteriaceae, the emergence of a new dominating COVID-19 variant, or poliovirus detected in sewage. The decision to start a control intervention requires balancing epidemic potential and expected or perceived burden of disease against the anticipated potential to contain or control an outbreak, feasibility, financial and social costs and acceptability. The disease burden will moreover depend on the pathogenicity of the infectious agent, level of exposure, and vulnerability the of host. The epidemic potential is determined by the transmissibility of the infectious agent and the environmental and behavioural context which makes a population more or less prone to transmit the infectious agent and susceptible for infection, including pre-existing (cross)immunity from natural exposure or vaccination (14). Systems and indicators need to be adapted to whether every single case should be searched and transmission interrupted, whether transmission from animals to humans should be prevented, or whether upsurges in hospital admissions should be anticipated (15).

Differential control interventions – precision public health

Most outbreaks are to some extent predictable, e.g., yearly malaria or RSV outbreaks, and control measures are in most cases well defined, effective and efficient. In low-resource settings, limited resources for surveillance and control measures can be quickly overwhelmed by competing threats and outbreaks. Focusing efforts on known areas or subpopulations where outbreaks start or where the impact is highest could free up capacity to deal with different threats.

Other outbreaks are unexpected, so experience is lacking in detection, risk assessment, and the implementation of proportional interventions, or surveillance data might be suboptimal, complicating the balancing of the outbreak's risks against interventions' benefits and harms. Potential harms of a public health intervention of which effectiveness is not known, should be considered, even though outbreak control indicators rarely consider the effect of a control intervention on other health issues beyond the concerned outbreak disease, general wellbeing or the environment. Interventions need to be appropriate, proportional, well targeted, and up- and downscaled according to the epidemiological context, to ensure effectiveness, adherence and future acceptance. The term precision public health has been coined for targeting interventions more effectively and efficiently to those populations most in need, based on surveillance data (16,17).

Increasingly rapid and abundant availability of surveillance data opens up possibilities for more differential control interventions, adapted to the current or foreseeable epidemiological situation. Most examples of differential interventions1 have been based on to the spatial distribution of incidence. The global cholera elimination strategy proposes to focus interventions on so-called hotspots, geographically limited areas, de facto based on local case incidence (18). For Human African trypanosomiasis control, active population screening is carried out in areas with high incidence. When incidence is low, surveillance falls back to passive case detection (19). When malaria incidence in areas in the Mekong region drops below 1 case per 1000 persons at risk, malaria control should shift from population-level interventions reducing transmission to individual malaria case investigations and entomological surveillance (20). Even though leprosy has a geographical focal distribution, the absence of uniform cut-offs for its endemicity have hampered tailoring control

[1] Following a literature search on PubMed for data-informed, focused, control interventions, using the search terms ("hotspot*" OR "hot spot*" OR "micro-epidemiology" OR "heterogeneity" OR "focal" OR "foci") AND ("elimination" OR "control" OR "Endemic Diseases"[Mesh] OR "Disease Eradication"[Mesh]) AND "Infections"[Mesh]

interventions (21). For tuberculosis, targeting geographical areas with higher tuberculosis incidence has been successful in Inuit communities in Canada in the 1950s and is currently used in control of MDR-TB in Peru (22). However, not only transmission, but also tuberculosis disease progression and mortality are strongly heterogeneous, affecting specific subpopulations. As a result, tuberculosis screening and treatment strategies target foreign-born individuals, household contacts of diagnosed cases, and other vulnerable groups (22). Also the spatial distribution of an animal host (e.g., rabies (23)), of a vector (e.g., onchocerciasis (24)) can be used to target control interventions.

Several of the above mentioned control strategies use various definitions of a 'hotspot' or 'transmission focus'. The identification of hotspots or foci based on incidence or other criteria can be challenging, prone to bias due to health care utilisation, reporting for surveillance, better diagnosis through targeted campaigns. E.g., for malaria, hotspots have been defined as transmission foci where individuals and households are at higher risk to be infected, and then transmit the parasite, quantified by the infection rate, measured from population antigen or serological testing (25). Cholera hotspots are currently solely based on incidence, but according to their definition, selecting hotspots should also be based on temporality of transmission (seasonal, continued throughout the year or interrupted), an area's role in spread to other areas, high case fatality rates, and vulnerability in terms of access to healthcare and to safe water and sanitation (18). Even though interventions targeting areas or populations differently have been proposed and researched for the control of many infectious diseases, most have not been translated to public health policies on a national or regional level.

Public health surveillance in low-resource settings

In many low resource settings, disease surveillance data is lacking, delayed, or not adequately interpreted, affecting the timeliness, effectiveness and proportionality of infectious disease control measures. Epidemiological capacity is needed to maintain and optimise robust surveillance systems, to translate data, and to assess risk, but is least available and developed in countries in Sub-Saharan Africa and in South Asia, which are the world's regions with the greatest disease burden per capita (26). An example: to this day, the impact of COVID-19 on excess mortality in LMIC and the African mainland remains unknown – nevertheless, also still debated in many industrialised countries. Except for South Africa and Egypt, no population-based mortality surveillance exists (27). The absence of valid and timely local data, representative of the total population, interferes with clear communication of the risk COVID-19 poses and it hampers decision-making based on balancing between risk of disease and the benefits and harms of an effective COVID-19 control measure, illustrated by difficulties in vaccination uptake (28).

In LMIC, surveillance systems do exist for a number of globally and nationally notifiable diseases, with official health care facilities regularly reporting cases meeting a case definition or confirmed by a laboratory. However, frequently health care is sought late or from private providers or medicine outlets, outside the healthcare provided by the government (12,29–33). In 2014, the share of healthcare financed by out-of-pocket payments of patient in LMIC was nearly 40%, in high-income countries 13% (34). Limited access to official health care impacts timely outbreak detection and skews disease burden estimates. Moreover, delayed access to or limited quality of health care hampers timely clearance of an infection through appropriate antimicrobial treatment, enabling further transmission to healthy carriers, patients, healthcare workers and the environment.

That many LMIC have community-based surveillance systems, such as Health and Demographic Surveillance Systems, or networks of community volunteers, offers opportunities for surveillance to inform health education, sensitization and control measures.

Synergies in the prevention and control of emerging infections and of antimicrobial resistance

The surveillance and control of antimicrobial resistance (AMR) can be largely based on the same epidemiological model of infectious disease outbreaks shown in the Figure, i.e. with compartments of the infectious disease process and determinants for exposure and disease progression. An outbreak of an AMR pathogen can be the result of transmission from a common source, human-to-human transmission, or from a change in host or environmental factors facilitating a jump from the gut or skin microbiome to the bloodstream within the host (35–37).

The spread of AMR has additional complexities. The emergence of an AMR microorganism can occur through permanent exchange of AMR genes between different microorganisms, including commensals in the human and animal gut, and microbes in the environment, e.g. through use of manure in agriculture (38,39). When microorganisms, in the human or animal gut, skin, blood, or environment, are exposed to antimicrobials, resistant microorganisms will survive, and such selective pressure can favour microorganisms with gene mutations encoding for AMR (40). The control of AMR therefore combines preventing the emergence of AMR genes or pathogens by limiting (suboptimal) antimicrobial exposure, and preventing onward transmission of AMR infectious agents by improving hygiene and sanitation, access to safe water, vaccination, timely diagnosis and effective treatment of infections (41).

AMR applies to any infectious agent that can develop resistance against antimicrobials, though the focus in this thesis is on resistance of bacteria against antibiotics, i.e. antibiotic resistance. In the industrialised world, community acquired infections are generally well controlled and the AMR burden is largely from healthcare associated infections (42). Moreover, the number of deaths from AMR infections has been decreasing there (43). Hospital-based interventions to optimise antibiotic use have shown to improve compliance to antibiotic policies, reduce the length of hospital stay, and safely reduce antibiotic use, in turn limiting colonisation or infection with AMR bacteria (44–46). Disability-adjusted life-years lost and deaths attributable to bacterial AMR are highest in South Asia and Sub Saharan Africa (47). In contrast to industrialised countries, in LMIC bacteria underlying invasive infections are predominantly community acquired (48). The elevated AMR prevalence there could be explained by the combination of frequent self-medication with antibiotics (12,33), elevated carriage of AMR bacteria in the gut and respiratory tract (49), and incidence of bacterial infections (50,51), increasing commensal and pathogenic bacteria's exposure to antibiotics. As a result, interventions should not be limited to healthcare-settings, and prevent as well transmission and selection of AMR pathogens in the community, by improving community-level antibiotic use, improving hygiene and sanitation in households, and preventing frequent contact with livestock animals dwelling in communities. This necessitates synergies in the prevention and control of emerging infections and of AMR.

In 2015, the World Health Organisation proposed a Global Action Plan against AMR with five strategic objectives: (1) to improve awareness through education and communication, (2) to improve knowledge through surveillance and research, (3) to reduce infections through sanitation, hygiene and infection prevention measures, (4) to optimise antimicrobial use, and (5) to increase investment in new medicines, diagnostics, vaccines and other interventions. AMR surveillance largely relies on the estimated prevalence of AMR among bloodstream infections surveillance, which may constitute a good proxy in industrialised countries where this largely matches the human AMR burden. Strict criteria can be used for sample collection, microbiological identification and antibiotic susceptibility testing, limiting the risk of selection bias compared to estimates from other collected specimens. In LMIC however, only a few secondary hospitals have clinical microbiology capacity and strict criteria for AMR surveillance. Moreover, limited or delayed access to those hospitals and frequent use of antibiotics prior to hospital admission result in selection biases and decreased sensitivity of blood cultures (52). Surveillance based on a key determinant of AMR, community-wide antibiotic

use, could more feasibly and timely inform AMR control interventions, in line with the Global Action Plan's fourth objective. For that purpose, since 2017, the World Health Organization classifies antibiotics in three groups, Access, Watch and Reserve, according to their intended availability and indications for use (53). Surveillance indicators, such as the ratio of Access vs. Watch group antibiotic quantity used, allow monitoring trends and comparison between healthcare facilities and between countries (54).

Objectives of this thesis

In this thesis, I analysed the effectiveness and timeliness of infectious disease surveillance systems informing infectious disease prevention and control, in a range of disease outbreaks and contexts, and proposed improvements or alternative data sources to use surveillance data more effectively.

Outline of this thesis

After the general introduction on infectious disease surveillance provided above, chapter 2 and 3 demonstrate shortcomings of clinical case definitions during Ebola and Yellow Fever outbreaks, delaying control measures, or missing cases. To speed up prevention and control measures and identify risk areas and populations to target with control measures, one option is to use surveillance and operational data from past outbreaks, as illustrated in chapter 4 for cholera, or to use risk behaviour data from ongoing control measures, illustrated in chapter 5 with COVID-19. Chapters 6 to 8 explore measurements of community-level antibiotic use, to inform AMR control measures in low-resource settings, monitoring risk rather than confirmed AMR infections – which is difficult and delayed in LMIC. We estimated the prevalence of self-medication with antibiotics in Sub-Saharan Africa in a systematic review (chapter 6). We assessed antibiotic use prior to hospital admission with persistent fever in Nepal, Cambodia, DRC, and Sudan from existing patient data (chapter 7). We then combined patient surveys after healthcare visits with household healthcare utilisation surveys to estimate provider type-specific and community-wide antibiotic use from different (formal or informal) healthcare providers in chapter 8. Finally, in a general discussion in chapter 9, I propose improvements, and explore alternatives or complements to infectious disease surveillance, in order to more timely and more effectively respond to several outbreak/AMR threats simultaneously.

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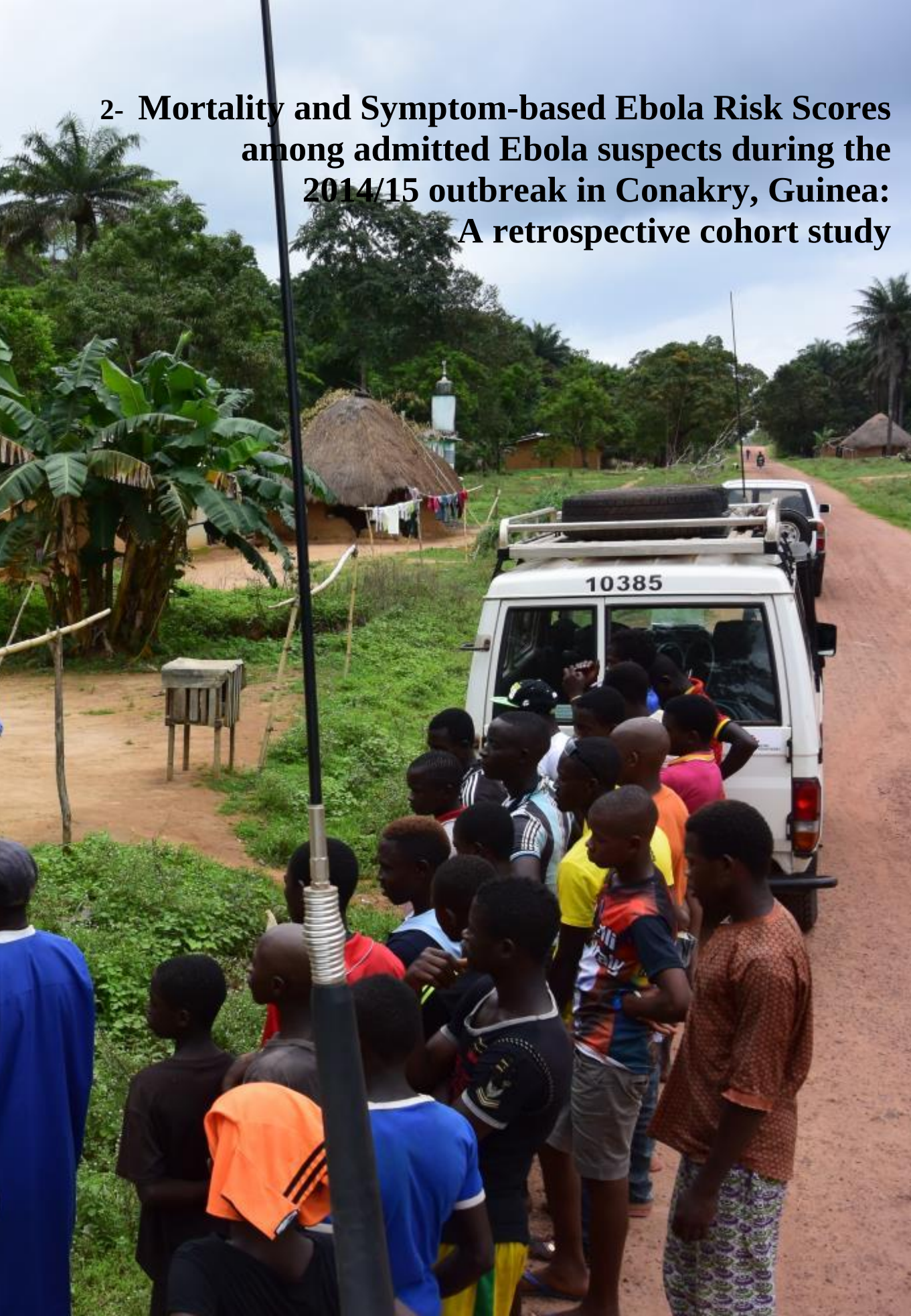
2- Mortality and Symptom-based Ebola Risk Scores among admitted Ebola suspects during the 2014/15 outbreak in Conakry, Guinea: A retrospective cohort study



Mortality among PCR negative admitted Ebola suspects during the 2014/15 outbreak in Conakry, Guinea: A retrospective cohort study

Published 30 June 2017 in Plos One. doi:10.1371/journal.pone.0180070

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Abstract

Non-cases are suspect Ebola Virus Disease (EVD) cases testing negative by EVD RT-PCR after admission to an Ebola Treatment Centre (ETC). Admitting non-cases to an ETC prompts concerns on case- and workload in the ETC, risk for nosocomial EVD infection, and delays in diagnosis and disease-specific treatment. We retrospectively analysed characteristics, outcomes and determinants of death of EVD cases and non-cases admitted to the Conakry ETC in Guinea between 03/2014 and 09/2015. Of the 2362 admitted suspects who underwent full confirmatory PCR testing, 1540 (65.2%) were non-cases; among them 727 needed repeated confirmatory PCR testing resulting in 2.5 days (average) in the ETC isolation ward. Twenty-one patients tested positive on the repeat test, most in a period of flawed sampling for the initial test and none after introduction of PCR confirmation with geneXpert. No readmissions following nosocomial EVD infection were recorded. No combination of symptoms yielded acceptable sensitivity and specificity to allow differentiating confirmed from non-cases. Symptoms as ocular bleeding/redness have high specificity, but limited usefulness as not common. Admission delay and age distribution were not different for both groups. In total, 98 (20.6%) of 475 deaths in the ETC were non-cases. Most died within 24 hours after admission. Living in Conakry (aOR 1.78 (1.08-2.96)) was the strongest risk factor for death. Weeks with higher admission load had lower case fatality among non-cases, probably because more acute (and treatable) illnesses of contacts of known cases were admitted. These findings show high numbers of potentially critically ill non-cases need to be considered when setting up triage and referral of EVD suspect cases. Symptoms and risk factors alone do not allow differentiating the non-cases. Integration of highly-sensitive EVD diagnostic methods with short turnaround time in the triage of peripheral hospitals and dropping the systematic 2nd PCR for symptomatic early presenters could limit delays in access to adapted care of cases and seriously ill non-cases. Whether feasible without compromising outbreak control, and under which conditions, should be further assessed.

Introduction

During the 2014/15 Ebola Virus Disease (EVD) outbreak in West Africa Ebola Treatment Centres (ETC) functioned not only as isolation and care unit for confirmed EVD patients, but also as triage point for any ill person possibly suffering from EVD. After anamnestic screening, patients meeting the EVD suspect case definition established by the Guinean Ministry of Health and World Health Organization (see Fig 1) were admitted to isolation wards for suspect patients, whilst waiting for definitive diagnosis by confirmatory EVD testing relying on reverse-transcriptase polymerase chain reaction (EBOV RT-PCR) (55). Upon result, confirmed cases were moved to separate isolation wards and non-cases (PCR negatives) discharged.

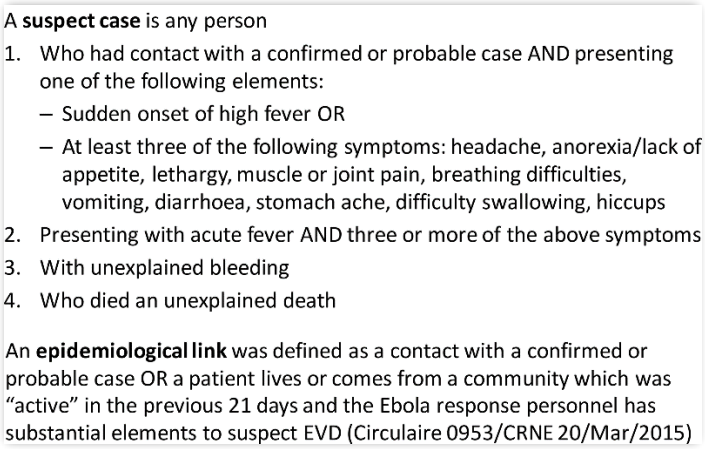

Fig 1. Ebola virus disease suspect case definition in Guinea (56)

In Guinea, the Conakry ETC was the main referral centre for the capital region with an estimated population of three million people. Between March 2014 and November 2015 when the last case was discharged, 2565 EVD suspects were admitted and tested by EBOV RT-PCR. In Conakry, even though secondary and tertiary health care facilities have continued to consult and admit patients throughout the outbreak, difficulties in determining the risk of exposure to EVD have resulted in delays in access to appropriate health care (57). Even after having tested negative for EVD, general health care facilities were not always willing to admit patients due to the potential risk of nosocomial infection.

The characteristics and case fatality of EVD confirmed cases have been widely described (58,59). On the contrary, for non-cases published literature is scarce and limited to the diagnostic performance of the EVD suspect case definition. Outcomes and risk factors associated with death of non-cases have not been studied before. The proportion of non-cases among EVD suspects is generally important though, as the case definition for EVD is very broad and includes symptoms common for a long list of possible differential diagnoses. In ETCs in Freetown and Kailahun, Sierra Leone and in Bong County, Liberia, 36%, 33% and 58% out of 850, 419 and 382 admissions respectively were PCR negative, and thus non-cases (60–62).

Beyond case- and workload, admission of non-cases in an ETC prompts also outcome-related concerns. Non-cases risk contracting a nosocomial EVD infection in the ETC suspect wards, where EVD-positive and negative individuals would be mixed in the same ward while waiting for PCR results. This remained a major concern throughout the outbreak, but so far no such nosocomial infections have been confirmed, even after investigation of patients who were readmitted after first having tested negative for EVD (60). In addition, an ETC stay may result, because of the limited diagnostic capacity and obligatory barrier care, in sub-standard care for non-cases with another urgently treatable disease.

Using routinely collected data of all suspect EVD patients admitted to the Conakry ETC in Guinea, we aimed to 1) describe the burden of non-cases in relation to the phase of the outbreak; 2) determine the duration of their stay at the ETC and (potential) subsequent nosocomial infections; and 3) compare characteristics, outcome and risk factors for death in confirmed cases and non-cases, in order to improve the selection, diagnosis and/or care of EVD suspects.

Methods

Study design and setting

Towards the end of the 2014/15 EVD outbreak in Guinea, we conducted a retrospective cohort study of all EVD suspects admitted to the ETC in Conakry between the first admission in the ETC on March 25th 2014, and September 14th 2015. The Conakry ETC was managed by Médecins sans Frontières and for most of the outbreak located within the Donka University Hospital, the largest health care facility in the country. In July 2015 the ETC was moved to a semi-permanent facility in another area of Conakry, Nongo.

Patient flow with diagnostic procedures

Patients presenting at the ETC triage were referred either from other health facilities, through follow up of contacts of known EVD cases, or presented spontaneously (self-referral). Upon arrival, patients were screened by history against the EVD suspect case definition (see Fig 1) by trained clinicians. If a patient did not meet the case definition, s/he was not admitted and referred to a general health facility or discharged home. If the case definition was met, the patient was admitted to the isolation ward for EVD suspect cases where a venous blood sample for confirmatory testing was taken and standard supportive care (antimalarial drugs, antibiotics) started.

EVD infection was confirmed using a quantitative RT-PCR assay to detect viral RNA. Between March 2014 and July 2015 confirmatory testing was carried out by the National Laboratory of Viral Haemorrhagic Fever at Donka University Hospital using Taqman RT-PCR assays on whole blood samples which run 40 cycles (i.e. reaching a Cycle threshold value of 40) (58). Results were available at a median of 5.6 hours (IQR 4.9-7.0) after blood sampling, which was done three times a day (63). Between January 28 and February 10 2015, for at least 43 patients, heparin instead of EDTA tubes have mistakenly been used when drawing blood (64). From May 2015 onwards the Xpert Ebola Assay (Cepheid GeneXpert Instrument Systems) was used, initially in parallel for validation and later as standard test to confirm EVD. The GeneXpert was operated in a laboratory within the ETC compound and blood sampling was no longer limited to three times a day, but performed upon arrival of the patient. GeneXpert testing allowed more rapid clinical decision making with results obtained within a median 2.7 hours (IQR 2.5 to 3.3 hours) after blood sampling (63).

If the RT-PCR test was positive, i.e. viral RNA was detected, the patient was transferred to an isolation ward for confirmed EVD cases. Patients who tested negative were discharged from the ETC, unless symptoms had started less than 72 hours prior to admission. For the latter, EVD was only ruled out after repeat PCR testing 72 hours after symptom onset. We use the term ‘non-cases’ for patients who were admitted as suspect cases in the ETC, but for whom EVD was definitively ruled out by diagnostic PCR.

Non-cases, alive at discharge, were sent home or transferred to a regular health care facility. Though guidelines foresaw the active follow-up of the discharged as EVD contact during the incubation period of a possible EVD infection contracted during his/her stay in the isolation ward, this was not always possible due to capacity constraints of the contact tracing teams. Follow-up on outcome of non-cases was limited to the time spent in the ETC while waiting for a definitive negative diagnostic EBOV-PCR. Data on deaths among non-cases which occurred after discharge from the ETC for the same illness episode were not available. For confirmed cases the outcome was documented for the entire course of illness (up to death or cure/discharge).

In addition to EVD diagnostic testing, the ETC laboratory also carried out Malaria rapid diagnostic tests (SD BIOLINE Malaria Ag P.f, Standard Diagnostics Inc.).

Data collection and analysis

Data were combined from routine case notification forms, patient medical files and laboratory results for all patients admitted during the study period. At triage, standardised notification forms were filled in by trained clinicians, recording history, symptoms upon admission and demographic characteristics. The date of symptom onset, type of referral, the outcome at discharge and the date of discharge were retrieved from copies of the medical files held outside the isolation ward. Outcomes at discharge from the ETC included death, discharged home (i.e. cured for confirmed cases), or referral. The outcome was unknown when a patient decided to leave the ETC before being discharged. For ten cases referred to another ETC (exclusively for health care staff) outcomes at discharge of the other ETC were added for the analysis. Referral of non-cases took place only after EVD infection had been excluded as described above.

Clinical and demographic characteristics and outcome at ETC discharge are reported as frequencies or medians with range and interquartile range. Differences in dichotomous variables between cases and non-cases were analysed using Pearson's Chi-squared test or Fisher's exact test (when less than five cases or non-cases presented the sign). Mann-Whitney U test was used for differences in age and in delay of admission. Sensitivity, specificity, positive and negative predictive value, crude positive and negative likelihood ratios were computed for every symptom or sign at admission. Risk factors for deaths were computed through bivariate and multivariate analysis using unconditional logistic regression in the form of odds ratios (OR). All variables tested in the multivariate model were categorized: age, sex, current residence, type of referral, case load in the ETC (below 50, or 50 or more ETC admissions in the week a patient is admitted), increases in case load (below 20, or 20 or more extra admissions as compared to the previous week) and the delay of admission. 95% confidence intervals and p-values were computed using Likelihood ratio tests. Statistical analyses were performed using R and Stata 12 [StataCorp. College Station, TX].

Only routinely collected programme data were collected, anonymized, and analysed. The Ebola intervention and Conakry ETC were a joint project of the Ministry of Health of Guinea and Médecins Sans Frontières. The study fulfilled the exemption criteria set by the Ethics Review Board (ERB) of Médecins Sans Frontières (MSF), Geneva, Switzerland.

Results

Admission rates and length of stay for cases and non-cases

Between 25 March 2014 and 14 September 2015, 2390 individuals were admitted as suspect EVD cases to the Conakry ETC. 2372 admitted patients underwent confirmatory testing. 822 (34.8%) were diagnosed with EVD, either after a single RNA positive EBOV RT-PCR test (n=801) or after a second test at least 72 hours after symptom onset (n=21). 1540 (65.2%) admitted suspects tested negative by RT-PCR and were designated as non-cases, following single (n=813) or repeated (n=727) negative RT-PCR. 18 patients chose to leave the ETC before any confirmatory testing and 10 underwent an initial PCR but evaded before a second test could confirm a diagnosis (Fig 2). Also 31 dead bodies of patients who died in the community or during referral to the ETC (including 7 EVD positive) were disposed at the ETC.

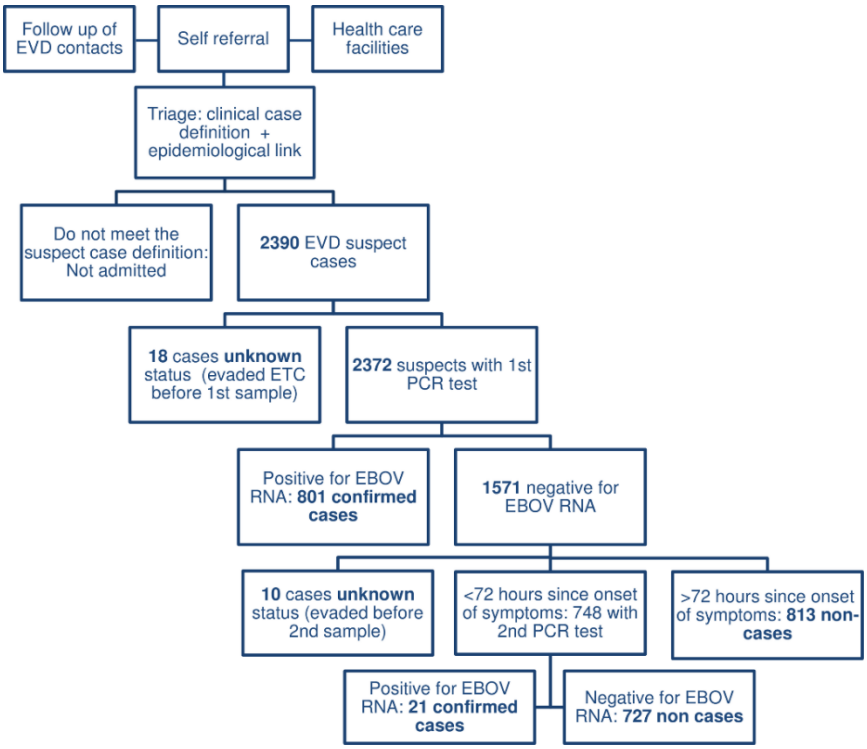

Fig 2. Case classification for suspect cases admitted to the Conakry ETC between March 25 2014 and September 14 2015.

The largest number of admissions to the ETC was seen in the last weeks of December 2014, with a peak of 92 admissions in epidemiological week 51, including 52 EVD confirmed cases, 39 non-cases and one unknown case. During the study period, a median of 9 confirmed cases (IQR 2-18) and 19 non-cases (IQR 13-29) were admitted per week. Admissions of confirmed cases outnumbered those of non-cases only at the start of the outbreak in March 2014 and when case-loads were highest in December 2014 (Fig 3). Over the outbreak, the number of admissions of non-cases has remained steadier than that of cases, mounting up to 10 or more non-cases admitted and tested each week, even in weeks with few or no confirmed cases.

31.7% (748/2362) of all EVD suspects or 47.2% (727/1540) of the non-cases underwent repeated diagnostic RT-PCR testing and therefore stayed longer than one day in the suspect isolation ward. Among the 822 confirmed EVD cases, 21 only got confirmed after that second RT-PCR test, thus yielding false negative initial PCR results. However, 14 of the 21 false negative first PCR tests occurred between January 28 and February 10 2015, when wrong sampling tubes (heparin instead of EDTA) were used. The remaining 7 false negative initial PCR tests all occurred before the incident. Two of those during one day in the beginning of the outbreak, and three occurred in the week with the highest caseload in December 2014. No false negative initial PCR results occurred after February 2015, on a total of 154 confirmed cases and thus none after introducing the Xpert Ebola Assay in May 2015, on 45 confirmed cases. Non-cases who needed only one PCR stayed on average 0.80 days (median 1; IQR 0 – 1; range 0 – 3), but those who needed a second PCR test to exclude EVD had to stay on average 2.49 days (median 2; IQR 2-3; range 1-5).

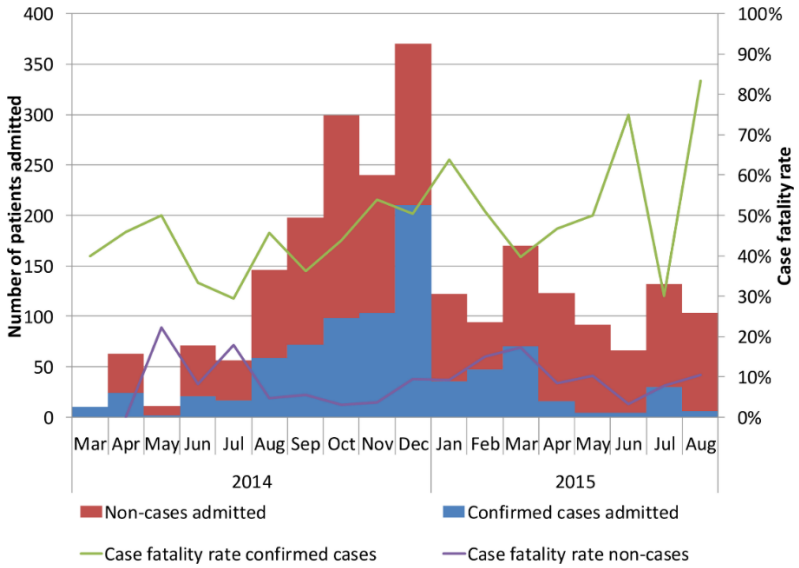

Fig 3. Frequency of admissions to the Conakry ETC and case fatality rates of EVD confirmed and non-cases each month between March 2014 and August 2015. Cases are classified according to outcome of confirmatory testing: cases confirmed by Ebola PCR, non-cases testing negative on EBOV PCR and cases with unknown status that left the ETC before being tested.

Four (initial) non-cases were readmitted. Three of them were also PCR negative at the second admission as suspect case. One patient who had tested PCR negative in the weeks with the tube incident, was readmitted a week after leaving the ETC, tested positive and died 6 days later.

Characteristics of confirmed EVD cases and non-cases

The age distribution among cases and non-cases was similar, though there were slightly more young children among the non-cases. Significantly more non-cases were male (61.7% vs 51.7%, p<0.001). The proportion residing in the capital region Conakry at the time of admission was higher for non-cases (67.9%) than for cases (54.9%, p<0.001).

The median delay between onset of symptoms and admission was similar. The longest delay recorded between onset of symptoms and admission for a case was 29 days, whereas a delay before admission of more than a month occurred in 6 non-cases.

Generalised fatigue and fever were the most common symptoms upon admission in confirmed and non-cases. Nausea or vomiting, diarrhoea, fatigue, loss of appetite, swallowing problems, joint aches, hiccups, unexplained bleeding and ocular redness/bleeding were less frequent among non-cases. Abdominal pain, headache, breathing problems, unexplained bleeding other than conjunctival bleeding, sore throat and coma were more frequent among non-cases (Table 1).

Table 1. Characteristics of confirmed EVD cases and non-cases upon admission

	Confirmed cases (%)	Non-cases (%)	p- value
Median age in years (IQR, range)	30.0 (20-41, 0-87)	28.0 (19-40, 0-96)	0.389
Age group			
1-4 years of age	43 (5.2%)	113 (7.4%)	0.031
5-18 years	112 (13.6%)	200 (13.1%)	0.913
18-49 years	543 (66.1%)	956 (62.6%)	ref
50 or more years	123 (15.0%)	258 (16.9%)	0.151
Male sex	51.7%	61.7%%	<0.001
Median number of **days between symptoms onset and admission** (IQR, range)	4 (2-6, 0-29)	3 (1-5, 0-61)	0.691
Clinical signs			
Fever	585 (71.5%)	1060 (69.5%)	0.300

Nausea/Vomiting	391 (47.8%)	640 (42.0%)	0.007
Diarrhoea	292 (35.7%)	423 (27.7%)	<0.001
Fatigue	693 (84.7%)	1168 (76.6%)	<0.001
Loss of appetite	515 (63.0%)	855 (56.1%)	0.001
Abdominal pain	231 (28.2%)	526 (34.5%)	0.002
Thoracic pain	61 (7.5%)	115 (7.5%)	0.942
Muscle pain	268 (32.8%)	441 (28.9%)	0.053
Joint ache	330 (40.3%)	528 (34.6%)	0.006
Headache	407 (49.8%)	835 (54.8%)	0.021
Cough	87 (10.6%)	201 (13.2%)	0.074
Breathing problems	21 (2.6%)	84 (5.5%)	0.001
Swallowing problems	89 (10.9%)	91 (6.0%)	<0.001
Sore throat[a]	4 (0.5%)	24 (1.6%)	0.026
Hiccups	84 (10.3%)	110 (7.2%)	0.011
Unexplained bleeding	206 (25.2%)	325 (21.3%)	0.033
Ocular redness/bleeding[b]	170 (20.8%)	130 (8.5%)	<0.001
Other	62 (7.6%)	229 (15%)	<0.001
Coma	7 (0.9%)	58 (3.9%)	<0.001
Skin rednessa	15 (1.0%)	3 (0.4%)	0.137
Photosensitivity or ocular paina	0 (0.0%)	2 (0.1%)	0.546
Confusion or disorientationa	2 (0.3%)	15 (1%)	0.070
Jaundice	0 (0.0%)	0 (0.0%)	
Type of referral[c]	n=25156 (22.3%)	n=620228 (36.8%)	<0.001
ETC ambulance	57 (22.7%)	116 (18.7%)	
Self-referral	78 (31.1%)	145 (23.4%)	
University hospital	1 (0.4%)	27 (4.4%)	
Not recorded	59 (23.5%)	102 (16.5%)	
Current residence			<0.001
Conakry (capital)	451 (54.9%)	1045 (67.9%)	
Outside Conakry	371 (45.1%)	486 (31.6%)	
Health care worker	99 (12.0%)	106 (6.9%)	<0.001

IQR, Interquartile range

[a] Fisher's exact test was used to compute the p-values when the n below five among either cases or non-cases.

[b] Ocular redness/bleeding refers to conjunctivitis and conjunctival bleeding. Data were not recorded separately.

[c] The type of referral was recorded from December 18 2014 onwards and in the analysis of referral type only admitted suspect cases from within Conakry were considered

Table 2 shows crude positive and negative likelihood ratios for EVD confirmation of the clinical signs. Only suspects with ocular redness/bleeding were more than twice more likely to be cases than to be non-cases (positive likelihood ratio of 2.44). Ocular redness/bleeding was present among 20.8% of confirmed cases. Suspects with breathing problems, sore throats, coma, skin redness and confusion or disorientation were more than twice more likely to be non-cases than to be cases (positive likelihood ratio below 0.5). These latter symptoms were rare though, all present in less than 6% of non-cases. The negative likelihood ratios did not yield differences of a factor 2.

Table 2. Clinical predictors of EVD confirmation when admitted to the Conakry ETC: sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios

Clinical signs	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)	Negative Predictive value (%)	Likelihood Ratio Positive	Likelihood Ratio Negative
Fever	71.5	30.5	35.6	66.7	1.03	0.93
Nausea/Vomiting	47.8	58	37.9	67.5	1.14	0.90
Diarrhoea	35.7	72.3	40.8	67.7	1.29	0.89
Fatigue	84.7	23.4	37.2	74.1	1.11	0.65
Loss of appetite	63.0	43.9	37.6	68.9	1.12	0.84
Abdominal pain	28.2	65.5	30.5	63.0	.82	1.10
Thoracic pain	7.46	92.5	34.7	65.1	.99	1.00
Muscle pain	32.8	71.1	37.8	66.3	1.13	0.95
Joint ache	40.3	65.4	38.5	67.1	1.17	0.91
Headache	49.8	45.2	32.8	62.7	.909	1.11
Cough	10.6	86.8	30.2	64.4	.807	1.03
Breathing problems	2.6	94.5	20	64.4	.466	1.03
Swallowing problems	10.9	94.0	49.4	66.3	1.82	0.948
Sore throat	0.5	98.4	14.3	64.8	.311	1.01
Hiccups	10.3	92.8	43.3	65.8	1.42	0.97
Unexplained bleeding	25.2	78.7	38.8	66.2	1.18	0.95

Ocular redness/bleeding[a]	20.8	91.5	56.7	68.3	2.44	0.87
Coma	0.9	96.1	10.8	64.5	.226	1.03
Skin redness	0.4	99.0	16.7	65.0	.374	1.01
Photosensitivity/ocular pain	0	99.9	0	65.1	0	1.00
Confusion or disorientation	0.2	99.0	11.8	65	.249	1.01
Clinical criteria suspect case definition[b]	56.9	46.4	36.3	66.8	1.06	0.93
Three major signs[c]	27.7	79.1	41.5	67.2	1.33	0.91

[a] Ocular redness/bleeding refers to conjunctivitis and conjunctival bleeding

[b] The suspect case definition in Guinea's clinical criteria (when no epidemiological link can be established) are "Any person presenting with acute fever AND presenting three or more of the following: headache, anorexia/lack of appetite, lethargy, muscle or joint pain, breathing difficulties, vomiting, diarrhoea, stomach ache, difficulty swallowing, hiccups" or "Any person with unexplained bleeding".

[c] Presenting with three major signs as identified by Lado et al (62): intense fatigue, confusion, conjunctivitis, hiccups, diarrhea, or vomiting.

The clinical criteria of the suspect EVD case definition, thus not considering contact history (i.e acute fever and presenting three or more other specific signs, Fig 1) were met in 56.9% of cases and 53.6% of non-cases.

Mortality and associated risk factors among cases and non-cases

Among 822 confirmed cases and 1540 non-cases respectively 377 (45.9%) and 98 (6.4%) died during their stay in the ETC, thus non-cases accounted for 20.6% (98/475) of all deaths in the ETC. The median length of stay in the ETC between admission and death was 4 days (IQR 2-6, range 0-17) for confirmed cases. Most (58/98, 59.2%) non-cases died on the day of admission, 33 during the 2nd day in the ETC suspect ward and the remaining four on the 3rd or 4th day. After testing negative for EBOV PCR, 256 non-cases were transferred for further health care and no outcome after discharge from health care is known (Table 3).

Table 3. Outcome at discharge of the ETC for all admitted patients in the ETC Conakry between 25 March 2014 and 14 September 2015

Outcome	Confirmed case	Non-case	EVD PCR unknown	Total
Patients who died before admission	8	23	0	31
Patients alive upon admission	822	1540	28	2390
Discharged	444 (54.0%)	1180 (76.7%)	0	1624 (67.9%)
Died	377 (45.9%)	98 (6.4%)	0	475 (19.9%)
Transferred		256 (16.6%)	0	256 (10.7%)
Unknown	1 (0.1%)	6 (0.4%)	28	35 (1.5%)
Total	830	1563	28	2421

EVD, Ebola viral disease; PCR, Polymerase chain reaction

Table 4 summarizes, for specific patient characteristics, the case fatality rate and the strength of association with fatal outcomes in the ETC, among cases and non-cases. For non-cases, residing in Conakry was identified as independent risk factor for a fatal outcome in the ETC (aOR 1.78 95%CI 1.08-2.96). Non-cases were less likely to die when admitted during a week with 20 or more extra admissions than the previous week (aOR=0.31; 95%CI 0.17-0.58) or a week with 50 or more admissions (OR=0.61; 95%CI 0.38-0.96). Differently from cases, dying among non-cases was not significantly associated with age below five or over fifty. No interactions or important confounding was observed between the risk factors for mortality we recorded.

Table 4. Bivariate and multivariate analysis of the association with possible predictors for higher mortality in confirmed EVD cases and non-cases. Patients who died before admission were excluded from the analysis.

Risk factor		Confirmed EVD cases			Non-cases		
		Case fatality rate (%)	Crude OR of dying (95% CI)	Adjusted OR (95% CI)	Case fatality rate (%)	Crude OR of dying (95% CI)	Adjusted OR (95% CI)
Age group	0 to 4 y	69.8	2.85 (1.45-5.58)	3.22 (1.62-6.38)	2.7	0.58 (0.21-1.63)	0.69 (0.24-1.96)
	5 to 17 y	24.1	0.39 (0.25-0.62)	0.39 (0.24-0.62)	6.0	1.09 (0.59-2.04)	1.13 (0.60-2.12)

	18 to 49 y	44.6	ref	ref	5.5	ref	ref
	50+ y	63.4	2.14 (1.42-3.21)	2.10 (1.39-3.17)	9.3	1.62 (0.98-2.66)	1.54 (0.93-2.56)
Sex	Female	40.7	ref	ref	6.4	ref	
	Male	50.8	1.50 (1.14-1.98)	1.62 (1.21-2.16)	6.6	1.04 (0.69-1.56)	
Current residence	Conakry	41.6	0.68 (0.52-0.90)	0.67 (0.50-0.94)	7.1	1.72 (1.0-2.80)	1.78 (1.08-2.96)
	Other region	51.2	ref	ref	4.5	ref	ref
Caseload/ week	≥50 admissions	46.7	1.08 (0.82-1.43)		4.8	0.61 (0.38-0.96)	
	<50 admissions	44.0	ref		7.1	ref	
Increase caseload*	<20 admissions	46.3	ref		7.8	ref	ref
	≥20 admissions	45.0	0.94 (0.70-1.26)		2.9	0.33 (0.18-0.59)	0.31 (0.17-0.58)
Symptom onset to admitted	<5 days	42.2	ref	ref	6.1	ref	
	≥5 days	50.4	1.38 (1.04-1.82)	1.33 (0.99-1.79)	5.7	0.90 (0.57-1.43)	
Type of referral	Non specified ambulance	50.0 (n=56)	ref		4.0 (n=225)	ref	
	ETC ambulance	38.6 (n=57)	0.63 (0.30-1.32)		11.2 (n=116)	2.71 (1.15-6.39)	
	Self-referral	42.3 (n=78)	0.73 (0.37-1.46)		9.0 (n=145)	2.12 (0.90-4.97)	
	University hospital	0.0 (n=1)			3.7 (n=27)	0.83 (0.10-6.72)	
	Not recorded	57.6 (n=59)	1.36 (0.65-2.84)		17.6 (n=102)	5.24 (2.35-11.7)	
Healthcare worker	Yes	44.4	0.96 (0.63-1.47)		3.8	0.53 (0.19-1.49)	
	No	45.3	ref		6.5	ref	

* increase in the number of admissions comparing the current week to the previous week; EVD, Ebola viral disease; OR, Odds ratio; 95% CI, 95% Confidence interval; ref, reference; y, year; ETC, Ebola Treatment Centre; In the multivariate analysis model of the confirmed cases, adjustments were made for age (groups), sex, the delay between onset of symptoms and admission, and the current residence of the patient. For the non-cases adjustments were made for age (groups), the current residence of the patient and for an increase in case load.

Discussion

Little attention has been given to the non-cases, suspect cases that tested negative for EVD, despite serious challenges such as 1) the possibility of nosocomial EVD infection during their stay in the isolation ward, 2) additional workload in the ETC when a large number of non-cases also require care and blood sampling, 3) missed opportunities for emergency care for non-cases in need of intensive care for another condition, 4) the stressful experiences the concerned patients underwent during their stay in the ETC and 5) the difficult and delayed access to regular health care facilities when EVD can only be excluded in an ETC.

Our study highlights the importance of considering the non-cases when designing referral, diagnosis and care of EVD suspects. Almost two thirds of admitted EVD suspects were non-cases and one in five deaths occurring in the ETC was a non-case dying from another condition than EVD before RT-PCR results were available. Other ETCs have also reported high proportions of non-cases, ranging between 33 and 58% (60,62,65), although never as high as the 65% non-cases among admissions in Conakry. Our results show that about 30% of cases and non-cases are being admitted without fever, in part likely a result of the difficulty to accurately measure body temperature due to biosecurity measures at triage and in the isolation wards. The most frequent symptoms have small differences in frequency between confirmed and non-cases. Specific symptoms as ocular redness/bleeding, breathing difficulties, sore throat, coma, skin redness and confusion or disorientation yield positive likelihood ratios that could allow differentiating cases from non-cases but their rare occurrence limits their usefulness. From our data, it is unlikely that a combination of symptoms alone can yield sufficient sensitivity and specificity to replace the clinical signs as currently used. Other studies have proposed a combination of three or more specific signs (62), or using a prediction score combining risk factors and symptoms to determine which patients to admit to the ETC (61). Applying the combination of three or more of the symptoms proposed by Lado et al on this cohort, would yield

an even lower sensitivity of 27,7% but an improved specificity of 79.1%. Differentiating EVD based on the current clinical criteria is difficult but no viable changes to the EVD suspect case definition can be proposed from our data.

ETC inpatient mortality among non-cases in rural Liberian and Sierra Leonean ETCs was 5.4% and 4.7% respectively (61,65), both slightly lower than, but in range with the 6.4% we observed in the Conakry ETC. From the medical files we could not retrieve enough detail on diagnoses of non-cases who died within the ETC to conclude whether those deaths were avoidable. It is likely that the impact of speeding up diagnosis would be limited for moribund non-cases. Nevertheless, diagnostic specific treatment of non-cases was delayed due to the passage in the suspect isolation ward. As no follow up data after discharge or referral of non-cases were available, our data cannot provide the full impact on mortality of delaying treatment for certain conditions while waiting in the ETC for a negative EBOV-PCR.

In future EVD outbreaks, the current set-up requiring testing through RT-PCR after referral to a centralised isolation ward may continue to compromise diagnosis and care of non-cases and interfere and delay care of confirmed cases. Even with PCR confirmatory testing yielding results within 2 hours (63), hours to days are spent on patient transfer to an ETC and – for almost half of the non-cases, while waiting for a second PCR test in the isolation ward. Integrating point-of-care RT-PCR EVD testing as part of triage at the larger health care facilities, coupled with greater emphasis on keeping these general health facilities functional during outbreaks, and intensified health education to promote early care-seeking behaviour, would allow more rapid diagnosis and quicker access to appropriate care for any suspected EVD case.

We observed moreover that using the point-of-care Xpert RT-PCR Ebola Assay no EVD cases were missed when only a single confirmatory test would have been carried out. In the Conakry ETC most false negative initial PCR results, all before February 2015, were related to errors in the sampling tubes used. Of the remaining false negatives five out of seven occurred clustered over a few days, also possibly suggesting a quality problem. The Xpert RT-PCR Ebola Assay has been proven to be at least as performant as several common laboratory-based assays, with no false negative results reported in studies on whole blood samples (66–68). Additional reviews of data from the other major ETCs would allow to assess whether the rule of a second confirmatory test at least 72 hours after onset of symptoms should be maintained in all circumstances.

A case report of a false negative test of an asymptomatic high risk contact in Monrovia in September 2014 (69) argued for repeat testing. However, being asymptomatic, this was an exceptional case which would also have been detected when initial symptoms appeared, through a well-functioning contact tracing and follow up system. Cases testing negative in our study were admitted suspect cases, therefore presenting symptoms.

The one third of non-cases who lived outside Conakry had better chances for survival than those from Conakry. We assumed that referrals of severely ill non-EVD patients from the largest health care facilities in Conakry had a higher chance of dying, but our hypothesis was not confirmed from the limited records on the type of referral of suspect cases. Non-cases referred from further districts were more often contacts of known EVD cases referred by surveillance teams, and therefore in better health than critically ill patients referred from health care facilities.

Previous studies of confirmed cases found that younger age (below 5 years) or older age (over 50 years) are determinants for higher mortality among confirmed EVD cases (58,59,70,71), which our study confirmed. We did not notice this increased mortality in the youngest non-cases, but found

also an association - although weaker, between older age and death, likely due to more severe comorbid conditions other than EVD in referred elderly people. We also observed higher case fatality among male confirmed cases than among females, a difference we did not observe among non-cases. This is in contrast to what we would have expected, i.e. that pregnancies, a known risk factor among female cases, would in general have increased case fatality among females. Unfortunately since pregnancies were poorly recorded, we were not able to assess the effect pregnancy had on mortality.

The number of admissions of confirmed cases started to increase from August 2014, reaching its peak in December 2014 when bed capacity was fully reached and work load for the ETC staff was overwhelming. However, this was not mirrored by an increased case fatality rate among cases and non-cases during these weeks. Paradoxically a decreased case fatality among non-cases was seen in weeks with increasing admissions (from 7.9 to 2.9%). One would have expected that the extra work load could have a detrimental effect on case fatality during the busiest weeks or weeks with large increases in the number of admissions. Hypothetically, this might be due to severely ill non-cases with severe conditions being referred especially at times when the risk of nosocomial infection in the ETC is considered low, whereas in weeks with increased numbers of admissions proportionally more contacts of known EVD cases with acute illnesses are referred, and they have better chances of survival.

Although much feared, we found no cases of nosocomial EVD infection contracted while staying in the isolation ward for EVD confirmatory testing. Only one patient out of 1436 discharged or transferred non cases was readmitted and tested positive after the second admission. This patients' initial negative result was false negative following an error with the blood sampling tubes.

There are a number of important limitations to this study. We had no final illness-episode outcomes available for 256 (16.6%) of the 1540 discharged non-cases, who were transferred to regular health facilities after EVD infection was excluded, which limits our case fatality findings. We could only analyse deaths up to the moment of transfer from the ETC, probably underestimating the total number of deaths among non-cases. More detail on diagnosis and causes of death of non-cases may have provided more insight on how and what proportion of deaths among non-cases could have been averted. Another limitation is that other possible drivers for the large proportion of non-cases could not be assessed: When the population started to gain confidence in the ETC, patients for whom no care options were available elsewhere may have started seeking care in the ETC; During times with higher epidemic intensity health care facilities demanded ill patients to first get tested in the ETC.

Conclusions

Our findings on non-cases in Conakry, studied during most of the West African Ebola outbreak, highlight the importance of considering non-cases when setting up triage and referral of EVD suspect cases. Centralising triage at the ETCs comes at a cost: the majority of admissions are non-cases in need of treatment for other conditions, and even though non-cases were only admitted for a maximum of three days until EVD confirmation, mortality may have been different when these patients would have been immediately admitted to a hospital where stabilization and critical care, as well as diagnose-specific examinations and treatment can be practiced without the limits of full-barrier care.

No combination of symptoms with sufficient sensitivity and specificity to differentiate EVD cases from non-cases can be proposed from our data. Other options to consider to overcome delays in access to adapted care for cases and non-cases are 1) the integration of highly sensitive EVD diagnostic tests with short turnaround time in the triage at peripheral hospitals, or 2) speeding up the

diagnostic timeframe by dropping the second confirmatory EVD test for those presenting at the ETC and health care facilities less than 72 hours after symptom onset. This latter strategy should be backed up by a sound contact tracing and follow-up system. Both strategies need further research to ensure feasibility and that outbreak control is not compromised.

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Symptom-Based Ebola Risk Score for Ebola Virus Disease, Conakry, Guinea
Published 3 May 2018 in Emerging Infectious Diseases, doi:10.3201/eid2406.171812

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To the Editor: In their article in *Emerging Infectious Diseases*, Oza and colleagues propose a score to risk-stratify Ebola virus disease (EVD) suspect cases while patients in an Ebola treatment center await laboratory confirmation (1). The Symptom-based Ebola Risk (ESR) score consisting of 6 symptoms (conjunctivitis, diarrhea, nausea/vomiting, headache, difficulty breathing, loss of appetite) performed well in internal validation, but no external validation was done. We externally evaluated the proposed ESR score on 805 EVD-positive and 1,506 EVD-negative cases in the Conakry Ebola Treatment Center (ETC) (2).

The ESR score yielded an area under the curve (AUC) of 0.58 (95% confidence interval, 0.56–0.61), which is lower than the 0.83 (95% CI, 0.79–0.86) reported in the Kerry Town ETC (online Technical Appendix Figure, https://wwwnc.cdc.gov/EID/article/24/6/17-1812-Techapp1.pdf).

Using the proposed risk thresholds (i.e., low risk if score <0, medium risk if score = 0, and high risk if score >0), 371 (46%) EVD-positive patients of the Conakry ETC were classified as high risk and 647 (43%) EVD-negative patients as low risk. However, negative and positive predictive values were generally low (online Technical Appendix Table). Our findings underline the importance of external validation in various settings before risk scores are applied outside of the setting within which they were developed. The reasons for poor validation are not defined but could include differences in application of the general EVD suspect case definition –integrating contact history; in patient characteristics because organization and access to care for EVD and non-EVD illness was different –patients transferred from holding centers to Kerry Town ETC; in the quality of data collection –the score being based entirely on subjective self-reported symptoms; and in morbidity of EVD-negative patients.

Stronger efforts need to be made to incorporate the patient contact history into the predictive models. Point-of-care EVD diagnostic platforms can perform reliable confirmatory testing within 90 minutes (3). We argue that by integrating such rapid confirmatory testing in triage, healthcare providers can avoid classifying patients on their likelihood to be infected with Ebola virus while waiting for laboratory confirmation in future outbreaks.

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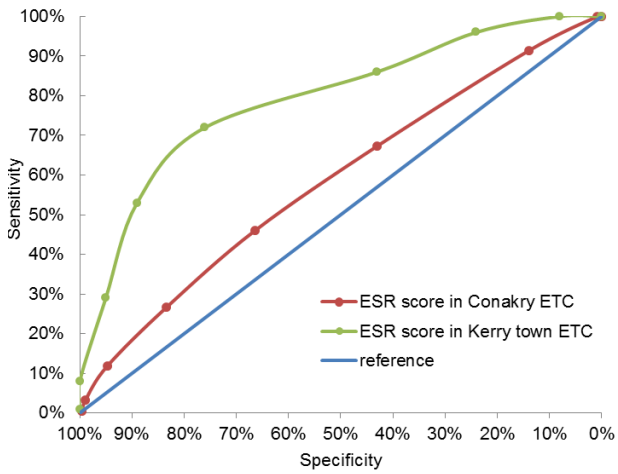
Technical Appendix

*Technical Appendix Table. Characteristics of Symptom-based Ebola Risk scores to predict Ebola virus disease confirmation among patients admitted to the Conakry treatment center, Guinea, 2014–15**

ESR score	% EVD negative	% EVD positive	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
≥-3	1	0	100 (100–100)	0 (0–0)	NA	NA
≥-2	13	9	100 (100–100)	1 (0–1)	35 (33–37)	100 (74–100)
≥-1	29	24	91 (89–93)	14 (12–16)	36 (34–38)	75 (70–80)
≥0	23	21	67 (64–71)	43 (40–46)	39 (36–41)	71 (68–74)
≥1	17	19	46 (43–50)	66 (64–69)	42 (39–46)	70 (67–72)
≥2	11	15	27 (24–30)	83 (81–85)	46 (42–51)	68 (66–70)
≥3	4	8	12 (10–14)	95 (94–96)	55 (47–62)	67 (65–69)
≥4	1	3	3 (2–5)	99 (99–99)	61 (46–76)	66 (64–68)
≥5	0	0	0 (0–1)	100 (99–100)	38 (9–76)	65 (63–67)

*ESR, Symptom-Based Ebola Risk; EVD, Ebola virus disease; PPV, positive predictive value; NPV, negative predictive value; NA, not available



Technical Appendix Figure. Receiver operating characteristic curves to identify risk for confirmed Ebola virus disease among patients admitted to the Conakry treatment center, Guinea, and to the Kerry Town treatment center, Sierra Leone, 2014–15.ETC, Ebola treatment center. The diagonal reference line indicates success expected on the basis of chance (AUC = 50%).

Page 30-31 : Yellow Fever case investigations. Matadi, DR Congo, June 2016. Photo by Brecht Ingelbeen

3- Urban Yellow Fever outbreak, Democratic Republic of the Congo , 2016. Towards more rapid case detection

Published 7 December 2018 in PLoS Neglected Tropical Diseases,
doi:10.1371/journal.pntd.0007029

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Abstract

Background

Between December 2015 and July 2016, a Yellow Fever (YF) outbreak affected urban areas of Angola and the Democratic Republic of the Congo (DRC). We described the outbreak in DRC and assessed the accuracy of the YF case definition, to facilitate early diagnosis of cases in future urban outbreaks.

Methodology/Principal Findings

In DRC, suspected YF infection was defined as jaundice within 2 weeks after acute fever onset, and was confirmed by either IgM serology or PCR for YF viral RNA. We used case investigation and hospital admission forms. Comparing clinical signs between confirmed and discarded suspected YF cases, we calculated the predictive values of each sign for confirmed YF and the diagnostic accuracy of several suspected YF case definitions. Fifty seven of 78 (73%) confirmed cases had travelled from Angola: 88% (50/57) men; median age 31 years (IQR 25–37). 15 (19%) confirmed cases were infected locally in urban settings in DRC. Median time from symptom onset to healthcare consultation was 7 days (IQR 6-9), to appearance of jaundice 8 days (IQR 7-11), to sample collection 9 days (IQR 7-14), and to hospitalization 17 days (IQR 11-26). A case definition including fever or jaundice, combined with myalgia or a negative malaria test, yielded an improved sensitivity (100%) and specificity (57%).

Conclusions/Significance

As jaundice appeared late, the majority of cases were diagnosed too late for supportive care and prompt vector control. In areas with known local YF transmission, a suspected case definition without jaundice as essential criterion could facilitate earlier YF diagnosis, care and control.

Author Summary

Yellow Fever is a mosquito-borne viral infection characterized by fever, followed after several days by jaundice, liver or kidney failure, shock or bleeding in up to 25% of cases. Although the virus primarily circulates in forests among primates, it can also be transmitted from human to human by mosquitoes in urban areas. If infected patients are detected early, they could benefit from timely supportive treatment, and control measures such as mosquito bite prevention, mosquito control, and mass vaccination campaigns, could prevent further spread of the disease. During 2015-16 a Yellow Fever outbreak spread in urban areas of Angola and DRC. The present study showed that most Yellow Fever patients that were diagnosed in DRC had travelled from Angola where they have been infected, and that most were adult men. Nevertheless, several patients have been infected locally, in urban settings in three provinces of DRC. Patients were diagnosed only when jaundice appeared,

more than a week after their illness started, too late to fully benefit from supportive treatment. During urban outbreaks, improving early access to healthcare and earlier detection of patients by recognizing acute fever when malaria infection is excluded, could improve Yellow Fever care and control.

Introduction

Yellow Fever (YF) is a mosquito-borne viral infection characterized by an initial non-specific flu-like phase that lasts for 3 to 6 days and includes fever, headaches and myalgia. In 15% - 25% of cases, a toxic phase follows with mild or severe jaundice, liver and kidney failure, which might lead to shock or bleeding (72,73). No specific treatment exists. Approximately half of the severe cases lead to death within 7 to 10 days (73,74). YF virus circulates primarily among forest-bound primates in a sylvatic cycle. Like other flaviviruses, YF can spread widely in urban areas, when transmitted from human to human by mosquito vector *Aedes aegypti* or potentially *Aedes albopictus* (75). Female mosquitos become infected from a blood meal of an infected human. The incubation period in humans is 3–6 days (76). Outbreak control relies on mosquito bite prevention, vector control, and mass vaccination campaigns. Early case detection by using an adapted case definition could allow earlier implementation of control measures for outbreak containment.

In the Democratic Republic of the Congo (DRC) each year a large number of sporadic YF infections occur following sylvatic transmission, when YF virus is transmitted by mosquitoes from non-human primates to persons living or working in forest areas (77). Because of limited mobility of patients infected in forest areas, YF transmission rarely reaches urban environments.

In December 2015 YF cases were detected in the Angolan capital Luanda. In March 2016, the outbreak in Angola intensified, resulting in cases spreading to bordering provinces of DRC and its capital Kinshasa (78). We carried out an investigation of the urban DRC outbreak to identify cases and describe the outbreak. Furthermore, we compared the performance of the case definition applied during the outbreak to alternative case definitions, aiming at an improved, timelier detection of cases in future urban outbreaks.

Methods

Study design and population

We present a detailed description of the 2016 YF outbreak in DRC and an analysis of the diagnostic accuracy of the case definition used, compared to alternatives. The YF cases related to this outbreak were reported to the national surveillance system between January and August 2016. In the analysis of the case definitions, we excluded vaccinated patients (at least ten days before symptom onset) and patients infected through sylvatic YF transmission (staying in a forest area in the two weeks to three days before symptom onset).

Case definitions and YF confirmation

During the outbreak in DRC, the suspected case definition for routine surveillance in DRC was used, as also proposed in WHO guidelines (79): an acute onset of fever followed by jaundice within 14 days after first symptoms onset. Any patient presenting at a healthcare facility meeting with this suspected case definition was notified to the Ministry of Health. Blood samples collected for every suspected case were tested for laboratory confirmation of Yellow Fever at the Institut National de Recherche Biomédicale (INRB), Kinshasa. A suspected case became confirmed when anti-YF IgM antibodies or YF viral RNA was detected in serum, if the patient was not immunized against YF. YF IgM detection consisted of an initial enzyme-linked immunosorbent assay (ELISA) to detect anti-flavivirus IgM antibodies, followed by a series of consecutive virus-specific ELISA tests to exclude other flavivirus infections such as Zika, dengue, and West Nile viruses. The ELISA results

needed to be further confirmed by demonstrating a four-fold increase in YF neutralizing antibodies or by a Plaque Reduction Neutralization Test. Simultaneously a RT-PCR assay tested the presence of YF viral RNA in the blood sample. A suspected case was discarded when neither YF specific IgM antibodies nor YF viral RNA were detected. Confirmed cases were further classified as imported or autochthonous relying on travel history to Angola within two weeks to three days before symptom onset. Current or recent malaria (co-)infection was tested during July-August 2016 among patients admitted to a YF management facility, through detection of P. falciparum HRP-2 antigen (SD BIOLINE Malaria Ag P.f, Standard Diagnostics Inc.).

Data sources

Patient demographics, symptoms, malaria co-infections, laboratory YF confirmation results, travel and vaccination history were extracted from case investigation forms (with suggested symptoms), patient medical files, and daily reports of notified suspected cases. Symptoms and malaria co-infections were systematically recorded in Kinshasa between 28 May and 02 August 2016, and thus only available for 14 confirmed cases and 97 discarded cases. GPS coordinates of places visited by patients while infectious, during the first 6 days after symptom onset, were used to map areas with possible ongoing transmission of YF.

Data analysis

We described recorded characteristics and deaths as frequencies, percentages or medians with interquartile range. We compared differences in frequencies between cases by using Pearson's Chi-squared test (or Fisher's exact test, as appropriate) and differences in median age using the Wilcoxon rank-sum test (when not normally distributed). We used QGIS 2.18 with OpenStreetMap shapefiles to generate a geographical dot distribution map of cases in Kinshasa. To avoid revealing the exact locations of the cases, we rounded longitude and latitude coordinates to 10^{-3} degrees, to assign a random point location within a 110m radius of the patients' recorded residences.

We identified potential predictors of YF by calculating positive and negative likelihood ratios (LR+ and LR-) for the presence or absence of every recorded symptom, severe anemia and a positive malaria test among confirmed and discarded cases for which those symptoms were recorded. LR+ is the increase in the probability of YF infection when the symptom is present, in other words sensitivity/(1-specificity) of that symptom to detect infection. LR- is the decrease in the probability of YF infection when the symptom is absent. We used combinations of predictive signs (LR+ or LR- larger than 2.5) to create new case definitions (four options). We drew receiver operating characteristic (ROC) curves to compare the diagnostic performance (sensitivity, specificity and Area Under the Curve (AUC)) of the DRC outbreak case definitions with our optional case definitions and those used in previous urban YF outbreaks in Uganda (2010/11), Brasil (2009) and Bolivia (1997/98) (80–82). We performed analyses in R 3.4.1 and STATA 12.

Ethics statement

The Ethical Review Committee at the University of Kinshasa approved the study (reference ESP/CE/049/2017). Only anonymized routine surveillance data, collected for the outbreak investigation was retrospectively analyzed. Therefore, no individual patient informed consent was asked.

Results

The Yellow Fever outbreak in DRC

Between 1 January and 11 August 2016, 2,269 suspected cases were reported in DRC. Of the 2,025 cases that underwent confirmatory testing, 78 (4%) were confirmed. Cases were confirmed in Kinshasa and two provinces neighbouring the Angolan border, Kongo-Central and Kwango. The

first confirmed case had onset of symptoms on 22 February, the final case on 12 July (Figure 1). Of the 78 confirmed cases, 57 (73%) were imported from Angola. Imported cases occurred mostly among adult male patients (Table 1): 88% (50/57) men; median age 31 years (interquartile rate (IQR) 25–37). Fifteen (19%) YF confirmed case patients had not travelled to Angola, and acquired YF in urban settings in Kinshasa (n=8), in the Angola-bordering Kwango (n=4), and Kongo-Central (n=3) provinces. Of these autochthonous cases 67% (10/15) were male; median age was 20 years (IQR 12–29; p<0.01). For six cases, no travel history could be retrieved (not classified). Six sylvatic cases, not related to this outbreak, were confirmed during the same period.

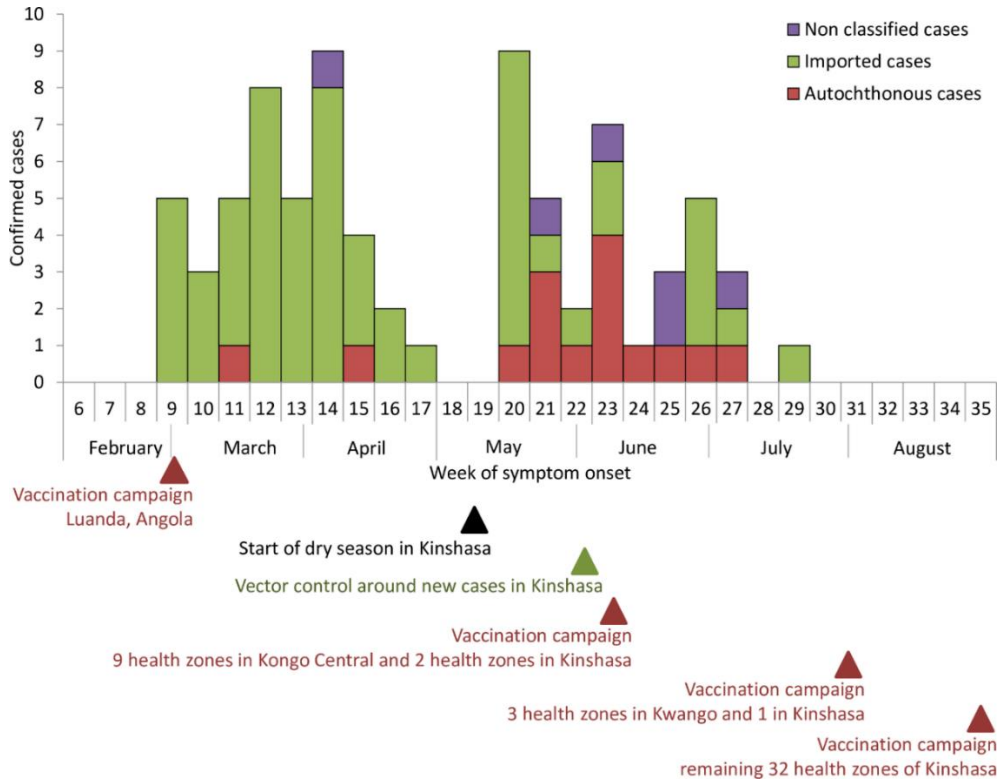

Figure 1. Weekly distribution of confirmed imported, autochtonous and non classified Yellow Fever cases, DRC, 2016.

Table 1. Patient characteristics and outcome among imported and autochthonous confirmed Yellow Fever cases, DRC, 2016.

Characteristics	Imported (N=57)		Autochthonous (N=15)		p value
	n	%	n	%	
Aged ≤5 years	0	0.0	1	6.7	0.20
Male sex	50	87.7	10	66.7	0.05
Hospitalized	25 (N=28)	89.3	7 (N=8)	87.5	0.89
Died	17	29.9	1	7.1	0.08
Living in district where autochthonous cases have earlier been diagnosed	6	10.5	4	26.7	0.11

Mapping the imported and autochthonous confirmed cases led to the identification of one geographical cluster of three autochthonous confirmed cases occurring between 30 May and 10 June 2016 in the same neighborhood of Kinshasa, where case investigations revealed another 3 deaths of suspected cases with symptom onset in the same period (https://osf.io/tk3gn/). This cluster was linked to a previously unidentified case who had returned from Angola with a fever 22 days before (8 May). All other cases were widespread, and could not be linked to one another.

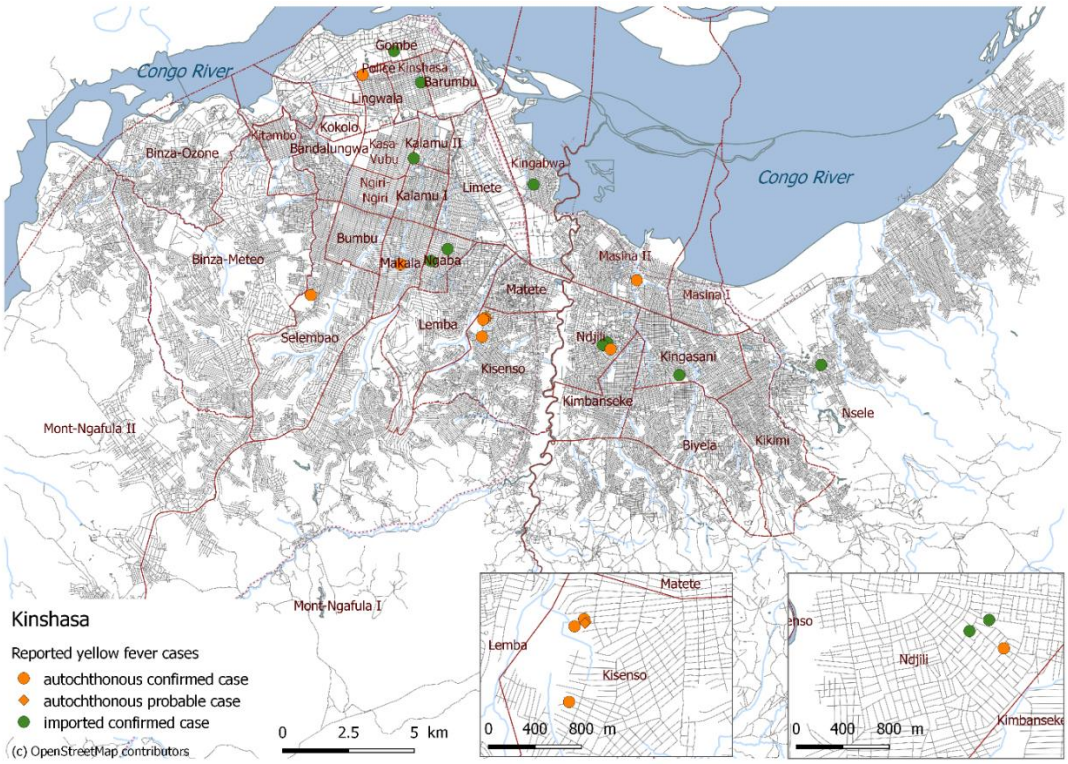

Figure 2. Geographical distribution of Yellow Fever cases in Kinshasa, DR Congo, 2016.

The median time from symptom onset to a first healthcare consultation in any healthcare facility was 7 days (IQR 6-9), to appearance of jaundice 8 days (IQR 7-11), to sample collection 9 days (IQR 7-14), and to hospitalization 17 days (IQR 11-26) (Table 2). The delay to sample collection was not significantly different (p=0.88) among imported and autochthonous confirmed cases.

Table 2. Median delays between symptom onset and seeking healthcare, Yellow Fever diagnosis, hospitalization and death among confirmed Yellow Fever cases, DRC, 2016.

Delay from symptom onset to…	**Median (days)**	**Interquartile range (days)**
Healthcare consultation (N=13)	7	6 – 9
Jaundice (N=5)	8	7 – 11
Suspected case notification and sample collection (N=77)	9	7 – 14
Hospitalisation (N=4)	17	11 – 26
Death (N=7)	15	10 – 16

Among the 74 confirmed cases tested by RT-PCR, 9 (12%) had detectable YF viral RNA. The blood samples of the 9 PCR-positive cases were collected at a median of 7 (range 1-14) days after onset of symptoms.

We recorded 18 deaths among confirmed cases, resulting in a case fatality of 23%. Confirmed cases died after a median of 15 days following the onset of symptoms.

Symptoms

Symptoms and malaria (co-)infection were recorded for 14 confirmed and 97 discarded cases from Kinshasa. The median age of those confirmed cases was 24 years compared with 31 years among confirmed cases without recorded symptoms (p=0.01); 64% and 86% (p=0.06) were male, respectively. The 97 discarded cases had a median age of 15 years, compared with 16 years among discarded cases without recorded symptoms (p=0.09); 53% and 56% (p=0.36) were male, respectively.

Thirteen (92.9%) confirmed cases had fever and 10 (71.4%) had jaundice (Table 3). Of symptoms not included in the routine suspected case definition, myalgia, vomiting and headaches were most frequently reported, respectively among 88.9%, 77.8% and 66.7% of confirmed cases. One had hemorrhagic signs. We identified no confirmed cases with severe anemia at admission. Of 9 tested confirmed cases, 3 (33.3%) were malaria co-infected. None (0/3) showed rapid clinical improvement after starting antimalarial treatment.

Table 3. Percentage, frequency and predictive value of signs/symptoms reported among confirmed and discarded Yellow Fever cases, DR Congo, 2016.

Clinical sign	Confirmed cases		Discarded cases		p-value	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)
	n/N	%	n/N	%			
Fever	13/14	92.9	93/97	95.9	0.61	1.0 (0.8-1.1)	1.7 (0.2-14.4)
Jaundice	10/14	71.4	93/97	95.9	<0.01	0.7 (0.5-1.0)	6.9 (2.0-24.6)
Bleeding signs	1/10	10.0	3/84	3.6	0.34	2.8 (0.3-24.4)	0.9 (0.8-1.2)
Diuresis decrease	4/10	40.0	7/80	8.8	<0.01	4.6 (1.6-12.9)	0.7 (0.4-1.1)
Myalgia	8/9	88.9	25/81	30.9	<0.01	2.9 (1.9-4.3)	0.2 (0.0-1.0)
Headache	6/9	66.7	46/81	56.8	0.57	1.2 (0.7-1.9)	0.8 (0.3-2.0)
Nausea	4/9	44.4	33/81	40.7	0.61	1.1 (0.5-2.2)	0.9 (0.5-2.0)
Vomiting	7/9	77.8	66/85	77.6	0.99	1.0 (0.7-1.5)	1.0 (0.3-3.6)
Epigastric tenderness	3/8	37.5	22/81	27.2	<0.01	1.4 (0.5-3.6)	0.9 (0.5-1.5)
Severe anaemia*	0/3	0.0	12/20	60.0	0.09	0.0	
Malaria HRP-2 positive**	3/9	33.3	73/90	81.1	<0.01	0.4 (0.2-1.0)	3.5 (1.9-6.6)
Malaria HRP-2 positive improving after treatment	0/3	0.0	11/13	84.6	0.02	0.0	

*Severe anemia as defined by WHO: a hemoglobin level of below 80 g/l, or below 70 g/l for pregnant women and children between 6 and 59 months old. ** HRP-2=histidine-rich protein II, an antigen expressed by *P. falciparum* trophozoites.

Diagnostic performance of the suspected case definition

Also 88 (91%) discarded cases had both fever and jaundice, i.e. the DRC suspected case definition, resulting in a 9% specificity of the case definition. Considering that 1,947 of 2,025 tested suspects were discarded, it had a positive predictive value of 3.2%. Of 90 tested discarded cases, 73 (81.1%) were malaria positive. Malaria positive discarded cases had a median age of 12 (IQR 5-20) years, with 67% being under 18 years old. Malaria negative discarded cases were older (p=0.03), median age 22 years (IQR 12-36), with 35% being under 18 years old. Of 13 malaria infected discarded cases, two (15.4%) did not improve after starting malaria treatment.

Decreased diuresis, myalgia and bleeding signs had the highest positive likelihood ratios, respectively 4.6, 2.9 and 2.8. Absence of malaria had the highest negative likelihood ratio, of 3.5.

When comparing the DRC suspected case definition with four case definitions based on the most predictive and frequent signs (Options A, B, C and D), and case definitions used during urban outbreaks, we found that a combination of fever or jaundice and myalgia or a negative malaria test (Option C), yields the best combination of sensitivity (100%) and specificity (57%) resulting in an AUC of 0.78 (Figure 3 and Table 4). Other combinations with early symptoms result in lower sensitivity, but improved specificity. The two 2010/11 Ugandan outbreak case definitions had better specificity than the DRC case definition, but at the cost of lower sensitivity (AUC 0.58 in 2010 and 0.69 in 2011). The 1997/98 Bolivia case definition improved sensitivity (79%), but did not improve the specificity (7%; AUC 0.43). The 2009 Brazil case definition was not substantially different from that in DRC to allow comparison.

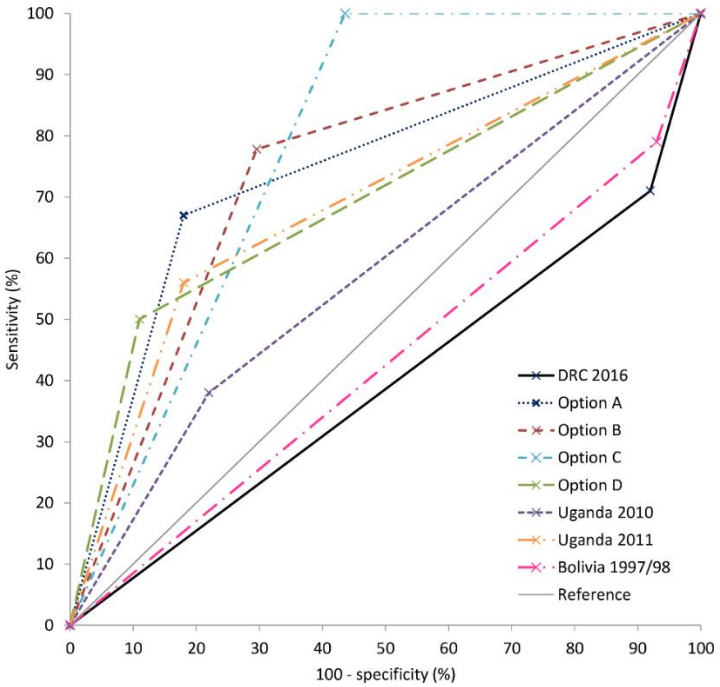

Figure 3. Receiver operating characteristic (ROC) curves of Yellow Fever suspected case definitions, applied on confirmed and discarded Yellow Fever cases with recorded clinical signs, DR Congo, 2016.

Table 4. Case definitions with sensitivity and specificity derived from the clinical signs of confirmed and discarded Yellow Fever cases, DRC, 2016.

Case definition	Description	Sensitivity (%)	Specificity (%)	Area under the curve (95%CI)
DRC 2016	Fever followed by jaundice (case definition applied during the DRC outbreak)	71	8	0.40 (0.27-0.52)
Option A	(Fever or jaundice) AND (malaria negative or not responding to malaria treatment)	67	82	0.74 (0.57-0.91)
Option B	(Fever or jaundice) AND myalgia	78	70	0.74 (0.59-0.89)
Option C	(Fever or jaundice) AND (malaria negative or myalgia)	100	57	0.78 (0.73-0.84)
Option D	(Fever or jaundice) AND (malaria negative or not responding to malaria treatment) AND (hemorrhage, decreased diuresis or myalgia)	50	89	0.69 (0.51-0.88)
Uganda 2010 (81)	1st stage (Nov-Dec) of the Uganda 2010/11 outbreak. Severe headache AND at least three of following: GI, dizziness, weakness, convulsions, unexplained bleeding	38	78	0.58 (0.39-0.77)
Uganda 2011 (81)	2nd stage (Jan-Feb) of the Uganda 2010/11 outbreak Acute onset of fever AND (malaria negative or not responding to malaria treatment) AND (jaundice or unexplained bleeding)	56	82	0.69 (0.51-0.86)
Bolivia 1997/98 (80)	Fever AND (jaundice or haemorrhagic symptoms or oliguria or death)	79	7	0.43 (0.32-0.54)

Discussion

Although >2000 suspected YF cases were reported and tested in DRC, only 78 cases were confirmed, with symptom onset between February and July 2016. The peak of the YF outbreak in DRC followed and mirrored the ongoing outbreak in Angola, and started to wane as vaccination went on in Angola. The majority of confirmed YF affected young men from DRC working in Angola, who returned to DRC to seek healthcare following a YF infection contracted in Angola. Despite evidence of 15 locally transmitted cases in three different provinces, we observed no widespread urban YF transmission, as in Angola. Possible reasons for this might be (i) the timing of

the first local transmission when the dry season took off, not allowing the vector carrying YF virus to replicate, (ii) the implementation of vector control measures around confirmed cases' homes, or (iii) the mass YF vaccination campaigns before the end of the dry season in the affected health zones.

Patients were diagnosed too late for effective supportive care and to guide potential vector control measures. By the time infected patients with severe symptoms received appropriate healthcare (median time to hospitalization 17 days after symptom onset), the 12 to 15 critical days to prevent death through supportive care had already passed (73,74). Several elements contributed to this delay: First, the majority of patients did not seek healthcare when going through the febrile phase of the disease within 5 days after symptom onset. YF testing is free in DRC but patients waited until symptoms worsened, afraid they might bear the cost of tests and treatments of other diagnosed conditions. Second, the suspected case definition applied during this outbreak encouraged notifying and testing only once jaundice appeared, 9 days after symptom onset. Finally, test results could take days to weeks because YF confirmatory testing was carried out in only one laboratory in the capital.

Low specificity of the DRC suspected case definition could only partially be explained by viral hepatitis. A 44% seroprevalence of viral hepatitis was found among suspected YF cases discarded during 2003-2012 in DRC (83). Dengue virus RNA and chikungunya virus RNA were found in respectively 3.5% and in 0.4% of those discarded YF cases during the same period (84). In our study, 81% of discarded cases were found to be malaria infected. Of those two thirds were children. This suggests that malaria may have been a leading cause of fever and jaundice among discarded cases in children.

A case definition in which jaundice would no longer be the main clinical criterion would allow more rapid detection of cases in districts where local transmission of YF is established. Nevertheless, considering that for each confirmed case another twenty suspected cases were notified and that no options for decentralized YF testing exist, other signs than fever are needed in the case definition to improve its specificity. Suspected case definitions used in previous urban YF outbreaks have relied on at least one severe sign occurring during the toxic phase of infection, and are therefore not more appropriate for timely diagnosis (80–82). When comparing the performance of different case definitions applied on the confirmed and discarded cases in our study, "fever or jaundice, and myalgia or a negative malaria rapid diagnostic test (or blood slide)" (Option C) provided the most robust combination of sensitivity and specificity. Once index cases and clusters of local transmission are identified in an area using the DRC/WHO case definition, a switch to case definition option C in the area with established YF transmission could speed up the identification of YF cases. Ideally, the case definition we propose should be externally validated against clinical data from ongoing or future outbreaks in a similar urban context.

A limitation to the comparison of case definitions is that our reference group is composed of discarded cases, which met the suspected case definition. Those were likely not representative of the source population (any patient presenting at a healthcare facility), and therefore, the calculated specificities are probably underestimated, limiting the external validity of our estimates. Second, our study evaluated the diagnostic performance of the suspected case definition using symptoms of only 14 (out of 78) confirmed and 97 (of 1947) discarded cases with symptoms systematically recorded. Although age and sex distributions were slightly different of those of confirmed cases without recorded symptoms, we think this may be due to chance. We did not expect any differences in clinical presentation to occur among slightly older adult cases, or among cases reported earlier during the outbreak. Therefore, we assumed the frequencies of symptoms we reported, were representative of all cases. Our sample of cases was however too small for a precise estimate of the proportion of cases failing to respond to malaria treatment when malaria and YF co-infected. Finally,

we were not able to quantitatively establish the improved timing of early diagnosis in our comparison of case definitions' diagnostic performance, because only for jaundice the timing of onset was recorded. Recording the time of onset of each symptom could have allowed to compare the case definitions' performance earlier through the course of the disease. Nevertheless, the case definition we proposed would probably have performed just as well when applied during the first days of illness, since fever and malaria infection would have been present already.

Due to the low accuracy of the case definition used during the 2016 YF outbreak in DRC and delays in accessing healthcare, most patients were diagnosed too late to receive beneficial supportive treatment and mitigate the complications of severe YF. Timely diagnosis of YF would also allow implementing vector control measures around confirmed cases' homes to prevent further transmission. Improving early access to healthcare and developing case definitions that do not include jaundice as essential criterion, in areas where urban YF transmission is established, will facilitate early case detection and management.

Acknowledgments

We acknowledge the invaluable role of chief medical officers and epidemiologists of the health zones of Kinshasa, Kongo Central and Kwango provinces, who reported suspected YF cases, spent long days investigating cases, and mobilized their communities for vector control activities. We thank Dr. Kostas Danis for final edits to the manuscript.

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Page 40-41: Cholera outreach, Maniema Province, DR Congo, October 2015. Photo by Brecht Ingelbeen

4- Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008-2017

Published 18 April 2019 in Emerging Infectious Diseases

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Abstract

In 2017, the exacerbation of an ongoing countrywide cholera outbreak in the Democratic Republic of the Congo resulted in >53,000 reported cases and 1,145 deaths. To guide control measures, we analyzed the characteristics of cholera epidemiology in DRC on the basis of surveillance and cholera treatment center data for 2008–2017. The 2017 nationwide outbreak resulted from 3 distinct mechanisms: considerable increases in the number of cases in cholera-endemic areas, so-called hot spots, around the Great Lakes in eastern DRC; recurrent outbreaks progressing downstream along the Congo River; and spread along Congo River branches to areas that had been cholera-free for more than a decade. Case-fatality rates were higher in nonendemic areas and in the early phases of the outbreaks, possibly reflecting low levels of immunity and less appropriate prevention and treatment. Targeted use of oral cholera vaccine, soon after initial cases are diagnosed, could contribute to lower case-fatality rates.

Introduction

The Democratic Republic of the Congo (DRC) accounts for an estimated 189,000 (5%–14%) of the 1.34–4.01 million cholera cases worldwide annually (1,2). Vibrio cholerae repeatedly reappeared in the DRC throughout the 1970s and became endemic around the Great Lakes in eastern DRC in 1978, resulting in part from favorable conditions for the bacterium's environmental survival (3–6). Complex emergencies in eastern DRC have since enabled the regular spread of cholera along the lake banks and to surrounding health zones, driven by water supply interruptions, high population densities, and population movement (5,7–9). In 2017, a countrywide cholera outbreak totaling >53,000 cases and 1,145 deaths was reported in DRC, affecting 20 out of 26 provinces, some of which had not seen cholera cases for more than a decade (10).

Cholera prevention and control rely on rapid outbreak detection, access to clean water, safe sanitation, dedicated treatment centers, and the targeted use of oral cholera vaccines (OCV) (11). We describe major cholera outbreaks that occurred in DRC during 2008–2017 to explore possible drivers for the spread of cholera in DRC and provide guidance for prevention and control interventions.

Methods

Study Design

We performed a retrospective analysis of cholera outbreaks from national cholera surveillance data and reference laboratory data collected from January (week 1) 2008 through November (week 46) 2017. In addition, we analyzed case management data collected during outbreaks in 2015–2017 from a selection of cholera isolation and treatment wards, called cholera treatment centers (CTCs).

Surveillance Data

Cholera is a notifiable disease in DRC and is therefore included in the national Integrated Disease Surveillance and Response System (IDSRS). The IDSRS is a syndromic surveillance system that compiles weekly morbidity and mortality reports, aggregated at the health zone level. These reports include weekly counts of suspected cholera cases and deaths, stratified into 2 age categories, <5 years and >/= 5 years.

The IDSRS uses 2 case definitions for a suspected cholera case, depending on whether a cholera outbreak has been declared by the Ministry of Health. During an outbreak, the definition is acute watery diarrhea with or without vomiting in a patient ≥ year of age; in nonoutbreak situations, the definition is severe dehydration or death following acute watery diarrhea in a patient ≥ 5 years of age.

Other Definitions

The World Health Organization (WHO) defines cholera hot spots as geographically limited areas where environmental, cultural, or socioeconomic conditions make transmission of disease easier and where cholera persists or reappears regularly (11). In DRC, hot spots are defined at the health zone level; 26 (5.0%) of 518 health zones across 6 of 26 DRC provinces are labeled as cholera hot spots according to WHO classification (D. Legros, World Health Organization, pers. comm., 2017 Nov 17). We considered a health zone's hot spot status to be stable throughout the study period. We defined a hot spot province as a province that included >1 hot spot health zones (Figure 1, panel A). A non–hot spot province was any province that did not contain any hot spot health zones.

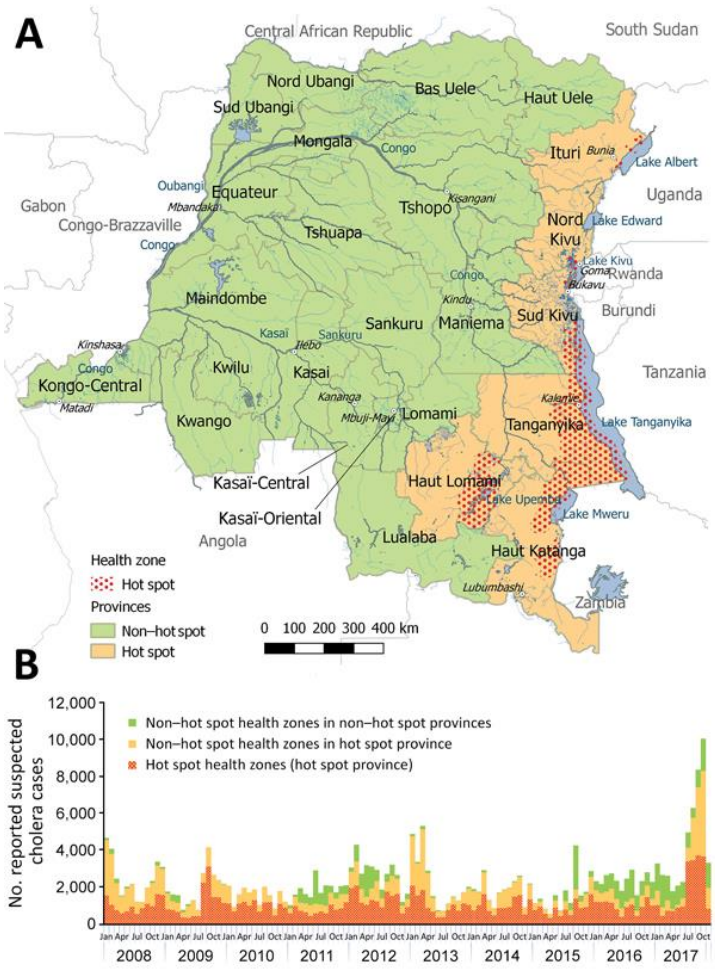

Figure 1. Hot spot and non–hot spot locations for cholera and number of suspected cases by location, Democratic Republic of the Congo, 2008–2017. A) Locations of cholera hot spot and non–hot spot provinces and hot spot health zones (2017 classification). B) Weekly number of suspected cholera cases. Case counts for 2017 are through week 46.

We generally defined an outbreak as follows:≥1 laboratory-confirmed cholera case and an increase in the number of suspected cases for ≥3 consecutive weeks. In the 3 provinces that consistently reported cholera cases all year (North Kivu, South Kivu, and Tanganyika), we applied a minimum threshold of 1,000 cases/week for ≥3 consecutive weeks. In the 2 provinces where sampling for laboratory confirmation was lacking (Ituri and Haut Lomami), we defined a major outbreak as any increase in the number of suspected cases for ≥3 consecutive weeks, reported by ≥3 different health zones.

Microbiological Data

The DRC national cholera reference laboratory, located at the Institut National de Recherche Biomédicale (INRB) in Kinshasa, carried out routine culture confirmation testing for national surveillance and outbreak confirmation purposes during the entire study period. Fecal samples or rectal swabs from patients with suspected cholera, which are usually collected at the beginning or end of suspected cholera outbreaks (12), were placed in either Carry-Blair transport medium or on filter paper and transported to the INRB for laboratory confirmation by culture. The following data were extracted from the laboratory database at INRB for each documented clinical sample: age, sex, health zone of residence, date of symptom onset, date of sample collection, date of sample receipt at the reference laboratory, and serotype result. Antimicrobial susceptibility testing was performed, from 2011 onward, by disk-diffusion testing according to Clinical and Laboratory Standards Institute M45-Ed3 (13), with testing of erythromycin instead of azithromycin and additional testing of fluoroquinolone antimicrobial drugs. Intermediate-susceptible isolates were grouped with resistant ones.

Case Management Data

Case management data were provided by 19 CTCs that Médecins sans Frontières had deployed in support of Ministry of Health cholera outbreak response activities, all in non–hot spot health zones, during 2015–2017. Médecins sans Frontières defines a case as >3 liquid stools in the previous 24 hours. From these line lists, we extracted age, sex, health zone of residence, date of symptom onset, date of admission to the CTC, and treatment outcome.

Population Data

We used population estimates by health zone for 2006 and 2016 provided by the Expanded Programme of Immunization to extrapolate the population of individual health zones for each year during 2008–2017, under the assumption of stable population growth. To ensure comparability of our data throughout the study period, we also used the DRC administrative divisions that were adopted in 2015 (26 provinces, instead of the previous 11) for 2008–2014 data.

Data Analysis

We analyzed weekly trends in the number of suspected cholera cases reported to the IDSRS, age and sex distributions, and case-fatality rates (CFRs) over the entire period, stratified by cholera hot spot status. We also calculated age and sex distributions for confirmed cases and cases admitted to CTCs, based on the reference laboratory register and CTC data. CFRs for persons with suspected cholera and for admitted patients were calculated with the cholera deaths as numerator (IDSRS data) and the suspected or admitted cholera cases as denominator (CTC data). We described the geographic spread of suspected cholera cases over time by mapping annual cumulative incidence rates by health zone. All reported cumulative incidence rates were expressed as suspected cholera cases per 100,000 population.

We performed data collation, cleaning, and analysis using Microsoft Excel, Stata 12.0, and R software. Maps were generated in QGIS 2.18 using OpenStreetMap shapefiles.

Ethics Statement

We analyzed databases that contained routinely collected and aggregated surveillance data and anonymized laboratory and patient admission data. For the use of patient admission data, we obtained ethics approval (ref. ESP/CE/034/2017) from the Kinshasa University Ethics Committee.

Results

General Description of Cholera Cases

During January 1, 2008–November 19, 2017, a total of 270,852 suspected cholera infections and 5,231 cholera-related deaths (CFR 1.9%) were reported in DRC in all 26 provinces. The largest cholera outbreaks were reported in 2008, 2009, late 2011 through 2012, early 2013, and late 2015 through 2017 (Table 1; Figure 1, panel B). Of the 9,510 (3.5%) suspected cholera cases for which the national reference laboratory received samples, 2,941 (30.9%), or 1.1% of all suspected cholera cases reported to the IDSRS, were laboratory confirmed for cholera.

Table 1. Suspected cases reported and number of samples collected, tested, and confirmed, countrywide, during cholera outbreaks, Democratic Republic of the Congo, 2008–2017

Location	Period	No. suspected cases			No. samples collected (positivity, %)			Serotype		
		<5	≥5	Total	<5	≥5	Total	Inaba	Ogawa	Hikojima
DRC	Jan 2008–Nov 2017	66,008	204,483	270,852	2,028 (34)	7,482 (30)	9,510 (31)	2,612	274	7
Reported outbreaks* in hot spot provinces										
NorthSouthKivu Tanganyika	Aug-Nov 2009	1,935	9,641	11,652	20 (50)	189 (33)	209 (35)	11	63	0
NorthSouthKivu Tanganyika	Aug–Nov 2017	6,653	14,709	21,362	5 (20)	41 (27)	46 (26)	5	7	0
Haut Katanga	Jan–Mar 2008	1,278	4,712	5,990	3 (67)	16 (50)	19 (53)	7	0	0
Haut Katanga	Jan–Apr 2013	1,935	6,504	8,441	1 (100)	11 (55)	12 (58)	4	3	0
Haut Lomami	Jan–Dec 2014	1,285	3,359	4,644	0	0	0	0	0	0
Ituri	Jan–Sep 2012	828	3,868	4,696	0	0	0	0	0	0
Reported outbreaks* in non–hot spot provinces										
Congo River	Jan2011-Dec12	2,809	11,878	14,686	89 (30)	578 (26)	667 (27)	179	0	0
Congo River	Sep 2015–17	4,991	20,330	25,422	123 (7)	633 (19)	756 (17)	118	10	0
Kwilu-Kwango-Kasai-Lomami-Sankuru	Jul–Nov 2017	374	2,123	2,497	0	10 (20)	10 (20)	1	1	0

Almost half of all suspected cholera cases (127,642; 47.1%) were reported in the 26 hot spot health zones and 224,212 (82.8%) in hot spot provinces. Of the remaining 46,640 suspected cases that were reported in non–hot spot provinces, 42,340 (90.8%) were reported during the outbreaks in 2011–2012 and 2015–2017.

Demographic Characteristics of Cholera Case-Patients

In hot spot health zones, 33,477 (26.2%) suspected cholera cases and 589 (28.4%) confirmed cholera cases were in children <5 years of age. In this age group, 23,615 (24.4%) suspected and 44 (14.4%) confirmed cases were reported in non–hot spot health zones in hot spot provinces and 8,916 (19.1%) suspected and 48 (10.8%) confirmed cholera cases in non–hot spot provinces. The median age of patients with confirmed cholera was 10 (interquartile range [IQR] 4–26) years in hot spot health zones, 20 (IQR 8–32) years in non–hot spot health zones in hot spot provinces, and 22 (IQR 10–36) years in non–hot spot provinces. Among CTC admissions in non–hot spot provinces, median age of the patients was 17 (IQR 5–32) years; 23% of those patients were <5 years of age. We observed an increase in the proportion of children <5 years of age admitted to a CTC: 19.0% in the first 4 weeks of the outbreak, >24.7% in weeks 5–8, 27.1% in weeks 9–12, and 34.5% in weeks 13–15. Male patients accounted for 51.4% of confirmed cholera cases and 50.2% of CTC admissions.

Case fatality

The CFR among suspected cholera cases was higher in non–hot spot provinces (4.5%) than in hot spot health zones (1.1%) and non–hot spot health zones located in hot spot provinces (1.8%). The CFR for suspected cases was lower for patients <5 years of age (911/66,008; 1.4%) than for those ≥5 years of age (4,331/204,483; 2.1%). We observed comparable distributions in CFRs by age for suspected cases when stratified by hot spot status (Table 2). Among CTC admissions in non–hot spot provinces, CFRs increased by age, from 2.4% (43/1,759) among children <5 years of age to 4.3% (32/752) among patients ≥50 years of age. CFRs decreased throughout an outbreak, from 5.1% (23/452) among CTC admissions in the first week of an outbreak to 4.4% (35/793) in the fifth week and 0.7% (3/429) in the tenth week.

Table 2. Case fatality rate (%) among suspect cholera cases, 2008–2017, and among patients admitted to a cholera treatment center, 2015–2017, Democratic Republic of the Congo

Criterion and location	Patient age, years	No. deaths	No. (%) cases	Case fatality rate, %
Suspected cholera cases				
Overall		5,231	270,852 (100)	1.9
Hot spot health zones	Total	1,407	127,642 (100)	1.1
	<5	292	33,477 (26)	0.9
	>5	1,116	94,082 (74)	1.2
Non–hot spot health zones in hot spot provinces	Total	1,745	96,570 (100)	1.8
	<5	301	23,615 (24)	1.3
	>5	1,440	72,777 (75)	2.0
Non–hot spot provinces	Total	2,079	46,640 (100)	4.5
	<5	318	8,916 (19)	3.6
	>5	1,775	37,624 (81)	4.7
CTC admissions				
Overall		267	9,076 (100)	2.9
Non–hot spot health zones in hotspot provinces	Total	3	1,294 (100)	0.2
	<5	0	357 (28)	0.0
	5–19	1	625 (48)	0.2
	20–49	1	241 (19)	0.4
	≥50	1	63 (5)	1.6
Non–hot spot provinces	Total	264	7,782 (100)	3.4
	< 5	43	1,759 (23)	2.4
	5–19	68	2,442 (31)	2.8
	20–49	104	2,609 (34)	4.0
	≥50	32	752 (10)	4.3

Geographic Spread in Hot Spot Provinces

Suspected cholera cases were reported all year in 3 of 6 hot spot provinces: North and South Kivu and Tanganyika, along Kivu and Tanganyika Lakes. Major outbreaks occurred in these provinces in 2009 and 2017. Both outbreaks started in August, peaked 6–8 weeks later, and decreased in intensity until the regions went back to baseline levels 5 months after the peak. Hot spot health zones constituting the lakeside cities of Goma (North Kivu) and Kalémie (Tanganyika) were first to report increasing case numbers, followed by adjacent non–hot spot health zones. The highest annual cumulative incidence among hot spot health zones was reported in Goma in 2017 (1,015 cases/100,000 inhabitants).

In the other 3 hot spot provinces, Ituri, Haut Lomami, and Haut Katanga, more sporadic outbreaks occurred. The largest outbreaks were observed in Haut Katanga in 2008 and 2013. Both outbreaks occurred during January–March; the 2008 outbreak counted 5,990 suspected cases and the 2013 outbreak 7,533 suspected cases. In both instances, most outbreak cases were reported in non–hot spot zones, in the cities of Lubumbashi and Likasi: 5,645 (94%) in 2008 and 6,534 (87%) in 2013. Haut Lomami Province reported smaller, but more frequent, outbreaks (every year, except in 2011);

the number of suspected cases varied from 690 in 2009 to 4,644 in 2014. Of the 19,975 suspected cases reported in Haut Lomami Province, 17,043 (85%) were from hot spot health zones around Upemba Lake. In 2017, non–hot spot health zones along the Lualaba River, a tributary of the Congo, also started to report cases. Ituri Province experienced a large outbreak during January–September 2012. Initial cases were reported in hot spot health zones along Lake Albert, followed by marked case increases in neighboring health zones.

Geographic Spread in Non–Hot Spot Provinces

In non–hot spot provinces, 2 major recurrent outbreaks occurred along the Congo River, the first in 2011–2012 and the second in 2015–2017. The outbreaks started in 2 different towns located in eastern, upstream provinces through which the Congo River flows: Kisangani (Tshopo) in March 2011 and Kindu (Maniema) in August 2015. From there, both outbreaks gradually progressed downstream in a westerly direction, consecutively reaching health zones in the provinces of Mongala, Equateur, Mai-Ndombe, Kinshasa, and Kongo Central (Figure 2). The elapsed time between the first reported outbreak cases in upstream provinces and those reported in Kongo Central, at the mouth of the Congo River, was 11 months for the 2011–2012 outbreak and 14 months for the 2015–2017 outbreak. Several provinces affected by the 2 outbreaks experienced a second, less intensive peak in suspected cholera cases approximately 1 year after the initial outbreak peaks. This dynamic was observed in several non–hot spot provinces: Tshopo in March 2011 and April 2012, Equateur in June 2011 and April 2012, and Mai-Ndombe in June 2011 and March 2012. Maniema Province experienced 2 such post-outbreak increases following an initial outbreak peak in September 2015: the first in January 2017 and a second in September 2017.

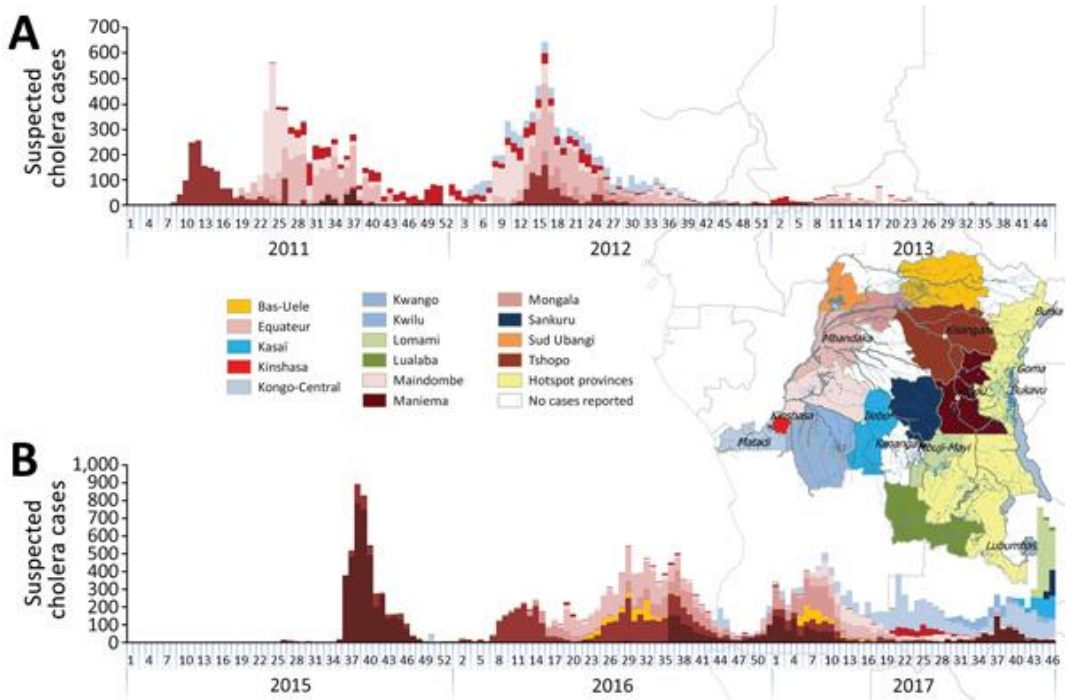

Figure 2. Weekly number of suspected cholera cases for non–hot spot provinces, Democratic Republic of Congo, 2011–2013 (A) and 2015–2017 (B). Colors differentiate provinces and correspond to the colors used in the overlaid map. Case counts for 2017 are through week 46.

In 2017, in addition to the downstream spread along the Congo, suspected cholera cases were reported in inland non–hot spot provinces where no cases had previously been reported during the

study timeframe (Figures 2, 3). In July 2017, cases were reported in Kwango Province, followed by Kasaï, Lomami, and Sankuru Provinces, upstream along the Kasaï and Sankuru Rivers.

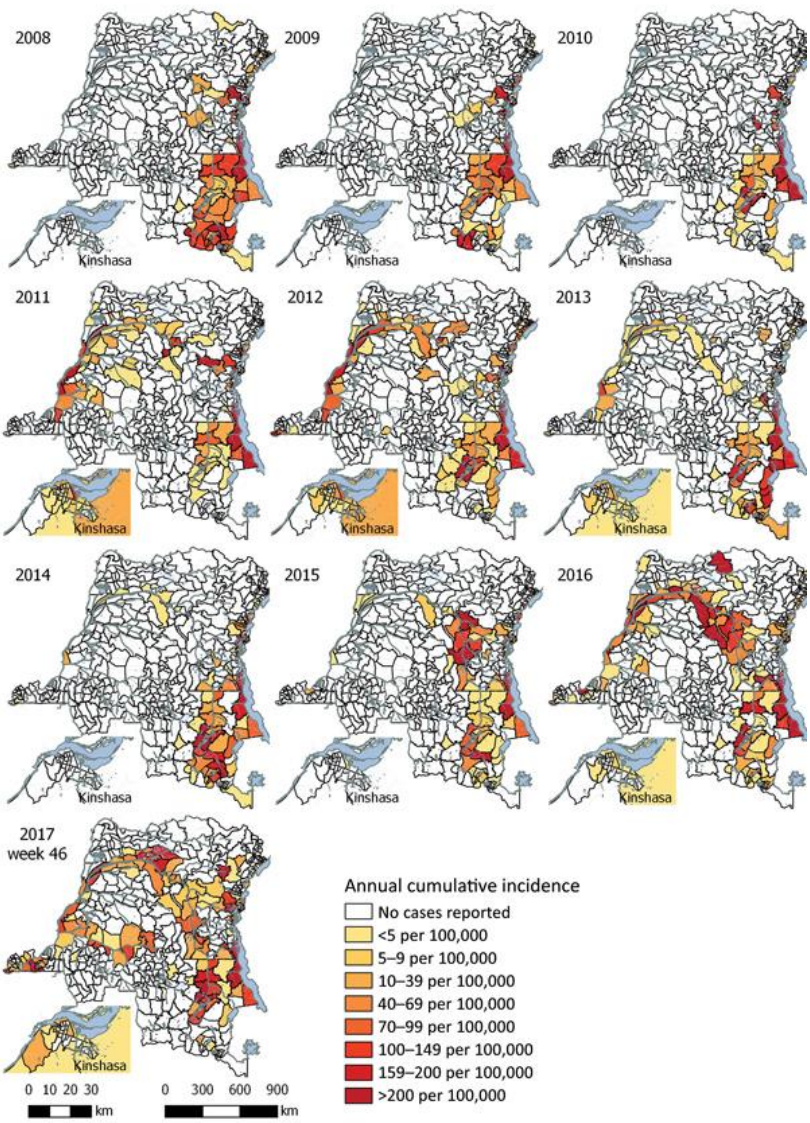

Figure 3. Annual cumulative incidence of suspected cholera cases reported per health zone, Democratic Republic of the Congo, 2008–2017. Case counts for 2017 are through week 46.

Along the Congo River, we observed the highest annual cumulative incidence rates in 3 different locations in 3 different years. The first came in 2011 in Bolobo (Mai-Ndombe, 1,107/100,000 population), the second in 2015 in Alunguli (Maniema, 1,088/100,000 population), and the last in 2017 in Kimpese (Kongo Central, 1,335/100,000 population).

Distribution of Cholera Serotypes

Serotyping data were available for 2,893 (98.4%) laboratory confirmed samples. Overall, Inaba was the most common serotype (90.3%), followed by Ogawa (9.5%) and Hikojima (0.2%) (Table 1). In the 2009 cholera outbreak in North and South Kivu and Tanganyika, the Ogawa serotype was detected in 84.0% of confirmed samples; in the 2017 outbreak, the Ogawa serotype was detected in 58.3% of confirmed samples. In the non–hot spot province outbreaks, the Inaba serotype was detected in 96.4% of confirmed samples. Although Inaba was the dominant serotype in the 2015–2017 nationwide cholera outbreak, Ogawa serotype cases were identified from August 2016 onward,

initially in the upstream Maniema Province, followed by reports further downstream in Tshopo Province in October 2016 and Kinshasa in July 2017.

Antimicrobial Resistance

Antimicrobial resistance testing yielded the following results: 99.2% (2,011 of 2,028 tested) were susceptible to doxycycline, 32.6% (642/1,993) to erythromycin, 99.1% (1,628/1,642) to tetracycline, 0.4% (8/2,029) to cotrimoxazole, and 96.9% (2,009/2,024) to ciprofloxacin. Of the 15 isolates that were resistant to ciprofloxacin, 14 were reported during 2016–2017.

Discussion

This 10-year retrospective analysis established 3 mechanisms of geographic spread contributing to the acute escalation of cholera in DRC in 2017: strong increases in the number of cases in cholera-endemic areas, the so-called hot spots, around the Great Lakes in eastern DRC; recurrent outbreaks spreading downstream along the Congo River; and the spread along branches of the Congo River that had been cholera free for at least the preceding 10 years. The observed geographic spread supports the hypothesis that the increased numbers of cases in cholera hot spots located along the Great Lakes functioned as incubators for major countrywide outbreaks (14–17). Coordinated and sustained cholera control interventions in these hot spot areas could be crucial for achieving cholera prevention, control, and elimination in DRC.

The 2011–2012 and 2015–2017 outbreaks followed a similar pattern: a spread from hot spots in the Great Lakes region to major cities located in the upstream section of the Congo River, then progressively spreading downstream, eventually reaching the country's densely populated capital of Kinshasa and Kongo-Central Province at the mouth of the Congo River. These outbreaks recurred in the same health zones over several years with peaks 1 year apart. Cholera propagation along major rivers has also been observed in Mali, Niger, Sudan, and the Central African Republic (17). Population movement and seasonal activities that increase human traffic and trade along the Congo River, and on the Great Lakes in particular, are likely to be key factors in such spread (16–18).

The range of circulating cholera strains in DRC, their origin, and their contribution to the epidemic remain unclear. During the 2011–2012 outbreak in nonendemic areas along the Congo River, fecal samples collected 1 year apart belonged to a single serotype and multilocus variable number tandem repeat analysis haplotype (19), suggesting that this outbreak was caused by a single cholera strain. Samples collected during the first year of the 2015–2017 outbreak affecting the same areas along the Congo River belonged to one serotype. The different serotype isolated 1 year later, which followed the same downstream spread to reach Kinshasa only after a year, probably suggests reintroduction of V. cholerae, rather than continued presence of the original V. cholerae through asymptomatic human carriers or an environmental reservoir in each of these communities living along the Congo River. In the hot spot provinces of DRC, several V. cholerae serotypes were simultaneously identified throughout the study period (Table 1), and isolates from several years grouped in 2 distinct multilocus variable-number tandem-repeat analysis haplotypes (19). This finding confirms the presence and role in these provinces of a V. cholerae reservoir, either the lakes or potential asymptomatic human carriers (7). In addition to gaining further insight into V. cholerae circulation, whole-genome sequencing studies could elucidate whether diversification of circulating strains contributed to the intensification of cases in cholera-endemic areas in 2017.

Our findings indicated that cholera outbreaks more disproportionately affected young children, particularly in hot spot provinces where preexisting immunity in the older population was possible. We also found that, although outbreaks along the Congo River affected all ages at the start of the outbreak, the adult population became gradually less affected in the subsequent weeks compared

with young children. This finding might suggest that children continued to be exposed more intensely than adults, that fewer adults remained susceptible to become ill after being infected, or that the case definition was less specific for children with watery diarrhea of other origin (non-Vibrio).

In a 2017 position paper, WHO recommended the targeted use of OCV in cholera-endemic regions, in humanitarian crises, and during outbreaks (11). The use of OCV in DRC has been limited so far to small-scale interventions: 120,000 persons in Kalémie (Tanganyika) in 2015 and 375,000 persons in 5 health zones along the Congo River in Kinshasa in 2016, attaining 90.0% vaccination coverage after a single OCV dose (A. Blake, Epicentre, Paris, pers. comm., 2017 Nov 14). OCV could be considered in several situations in DRC: in cholera hot spot health zones that report a notable increase in reported cases; in non–hot spot health zones adjacent to hot spot health zones, when such increases occur; in health zones along the Congo River, when surveillance reports cholera in upstream communities; during acute emergencies in non–cholera endemic areas of DRC where suspected cases are reported and confirmed; and in settings with particularly poor water and sanitation conditions. In 2015, only 31% of the population in rural DRC used a drinking water source protected from outside contamination, and 29% used sanitation facilities (20); targeted OCV can provide an effective additional means to control cholera in areas without good water and sanitation conditions.

Antimicrobial resistance testing results support the continued use of doxycycline to treat severe cholera (21) but indicate that cotrimoxazole and erythromycin (and probably azithromycin), which are alternate treatment choices, are unlikely to be very effective treatment options. Ciprofloxacin remains an alternate option to treat children (22), but the recent emergence of ciprofloxacin resistance needs to be monitored.

Some limitations apply to our study. Although the reporting of suspected cholera likely does not accurately reflect the full burden of cholera in DRC, it does allow for the documenting of trends and outbreaks. Zero case reporting is not required in the IDSRS, possibly leading to an underestimation of suspected cholera in our analysis, particularly for non–cholera endemic areas where health services might not as readily clinically diagnose and report cholera. Logistical constraints, the lack of an established and systematically implemented national sampling protocol, and limited resources (including an inconsistent availability of transport media) resulted in variable sampling and laboratory confirmation rates over time and place. A more systematic sampling and laboratory confirmation protocol could be developed on the basis of existing international guidelines (23) and possibly through the implementation of a decentralized cholera confirmation laboratory network. Our study considered hot spots to be stable throughout 10 years. When observing the affected provinces over the years, we found no indications that hot spots at the province level changed. However, at the health zone level, hot spots could have changed, which could have influenced some of our findings.

Focusing control efforts in DRC on hot spots would be an effective approach to reach elimination only if it can be done rapidly and effectively. Considering the context of conflict and instability in some of the hot spot health zones, a critical portion of the population in the hot spots may continue to be infected, and traveling of cases to nonendemic health zones will then give rise to new outbreaks every few years. Our study was able to identify several such highly vulnerable health zones that are at risk of recurrent outbreaks that could be avoided through the use of OCV, providing population immunity.

In conclusion, 2017 was characterized by an intensified epidemic along the Great Lakes of DRC, recurrence of an outbreak downstream of the Congo River, and an unexpected increase in cholera cases in inland regions of DRC where no cases had been reported for 15 years. Furthermore, ongoing conflicts in the cholera-endemic provinces remain a concern, hampering control efforts at the presumptive origins of outbreaks. Surveillance data adequately describe geographic spread and differences in CFRs, which can be used for targeting of cholera prevention and control actions. A policy for targeted vaccination of at risk populations is needed. Epidemiologic and phylogenetic studies of historical and circulating cholera strains could provide further insight into how cholera spreads from one community to others.

Acknowledgment

This study was financed by the Outbreak Research Team of the Institute of Tropical Medicine, Antwerp, Belgium, and the ECDC Fellowship Programme.

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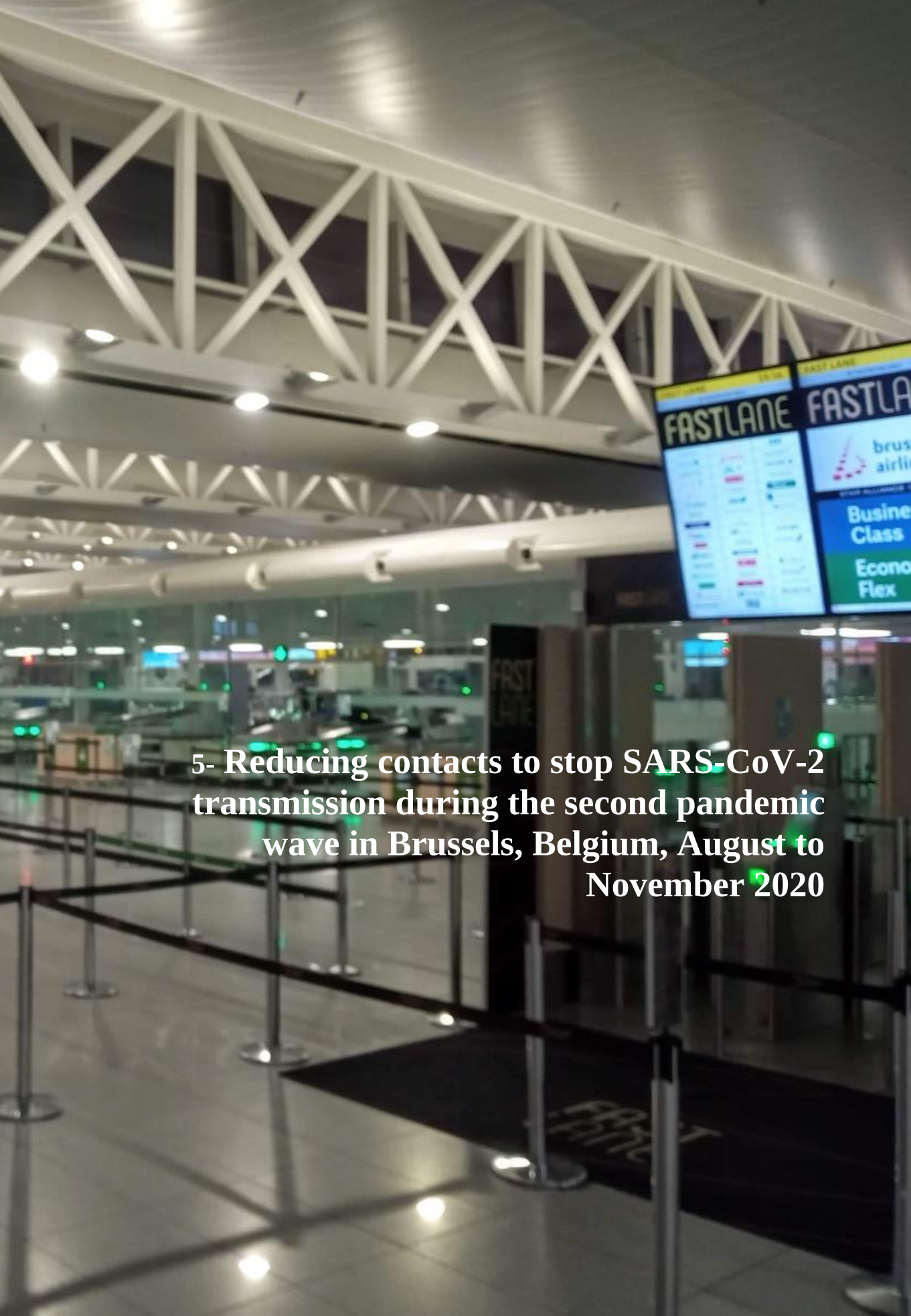
Page 52-53: Brussels airport, December 2020. Photo by Brecht Ingelbeen



5- Reducing contacts to stop SARS-CoV-2 transmission during the second pandemic wave in Brussels, Belgium, August to November 2020

Published on 18 Feb 2021 in Eurosurveillance, doi:10.2807/1560-7917.ES.2021.26.7.2100065

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Abstract

To evaluate the effect of physical distancing and school reopening in Brussels between August and November 2020, we monitored changes in the number of reported contacts per SARS-CoV-2 case and associated SARS-CoV-2 transmission. The second COVID-19 pandemic wave in Brussels was the result of increased social contact across all ages following school reopening. Physical distancing measures including closure of bars and restaurants, and limiting close contacts, while primary and secondary schools remained open, reduced social mixing and controlled SARS-CoV-2 transmission.

Introduction

Belgium reported per capita the highest number of coronavirus disease (COVID-19)-related deaths and near highest number of cases worldwide and was heavily affected during Europe's first and second pandemic wave, reporting a total of 21,634 deaths and more than 700,000 cases on 13 February 2021 [1]. We describe the effect of physical distancing and school reopening on the number of contacts reported by each confirmed case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and on associated age-specific SARS-CoV-2 transmission patterns, using operational data from the COVID-19 contact tracing system of the Brussels region (Supplementary material) and case reports made available via the Belgian institute for health, Sciensano.

Physical distancing measures in summer and autumn

An increase in COVID-19 cases in July 2020 in Antwerp, Belgium's second largest city, was reverted following a provincial ban on indoor events involving more than 100 people, a curfew, mandatory teleworking, mandatory wearing of face masks, and a national limit of five close contacts per household. Close contacts were individuals outside the household, with whom one could have contact for more than 15 min without keeping a distance of 1.5 m and not wearing a mask, excluding children younger than 12 years. However, soon after the end of the summer holidays, while case numbers were rising again, national and regional governments loosened physical distancing measures. Belgium's Brussels-Capital region was first to observe a steep increase in cases but also to re-introduce physical distancing measures (Table).

Table. Physical distancing measures and SARS-CoV-2 testing policy changes, Brussels region, July–November 2020

Intervention	Start date
Cafés and restaurants may remain open until 1:00 and can take maximum 10 people per group	8 June
Sports allowed in groups of maximum 50 people	8 June
Maximum five close contacts[a] per week	30 July
Reopening primary and secondary schools	1 Sep
Restart universities at 50–75% room occupancy, with face masks	14 and 21 Sep
Limit on number of close contacts suspended	30 Sep
Quarantine for high-risk contacts[b] reduced from minimum 10 days to 7 days (if two negative tests)	30 Sep
Maximum three close contacts per week	6 Oct
Recommended teleworking	6 Oct
Bars and cafés closed at 23:00	6 Oct
Bars and cafés closed	8 Oct
Universities restrict seat occupancy to 20%	19 Oct
Testing restricted to symptomatic suspected SARS-CoV-2 cases (except for healthcare workers)	21 Oct

Quarantine for high-risk contacts extended to 10 days	21 Oct
Restaurants closed	26 Oct
Maximum one close contact outside the household per person and maximum four people in private gatherings (excluding < 12-year-olds)	26 Oct
Curfew between 10:00 and 18:00	26 Oct
Teleworking becomes the rule	26 Oct
Indoor sports prohibited (except < 12-year-olds)	26 Oct
Universities gradually switch to online learning	26 Oct
Maximum one close contact outside the household per household	2 Nov
Mandatory teleworking	2 Nov
Non-essential shops closed; professions involving physical contact or gatherings suspended	2 Nov
Extended autumn school holiday (31 Oct–15 Nov)	31 Oct

[a] Close contacts are persons who are not part of your household, with whom contact can last for more than 15 min without keeping a distance of 1.5 m and not wearing a mask, excluding children younger than 12 years.

[b] High-risk contacts are persons with whom the SARS-CoV-2 PCR-positive case had physical or cumulative 15 min non-physical contact within 1.5 m from 2 days before to 7 days after onset of symptoms.

Sources: https://www.commissioner.brussels/updates-covid-19**;** https://covid-19.sciensano.be/nl

The second COVID-19 pandemic wave in Brussels region

From 1 August to 12 November 2020, Brussels-Capital region reported 63,838 confirmed SARS-CoV-2 cases (5.2% of a population of over 1.2 million [2]), i.e. RT-PCR positive, among 415,412 SARS-CoV-2 PCR tests performed. The daily number of confirmed cases peaked on 20 October with 2,950 reported cases (Figure 1). SARS-CoV-2 test positivity was highest among 20–29-year-olds (7.4%, 13,436/181,940) and decreased with age to 4.3% positivity (4,913/114,637) among those 70 years and older (Supplementary Figure S1).

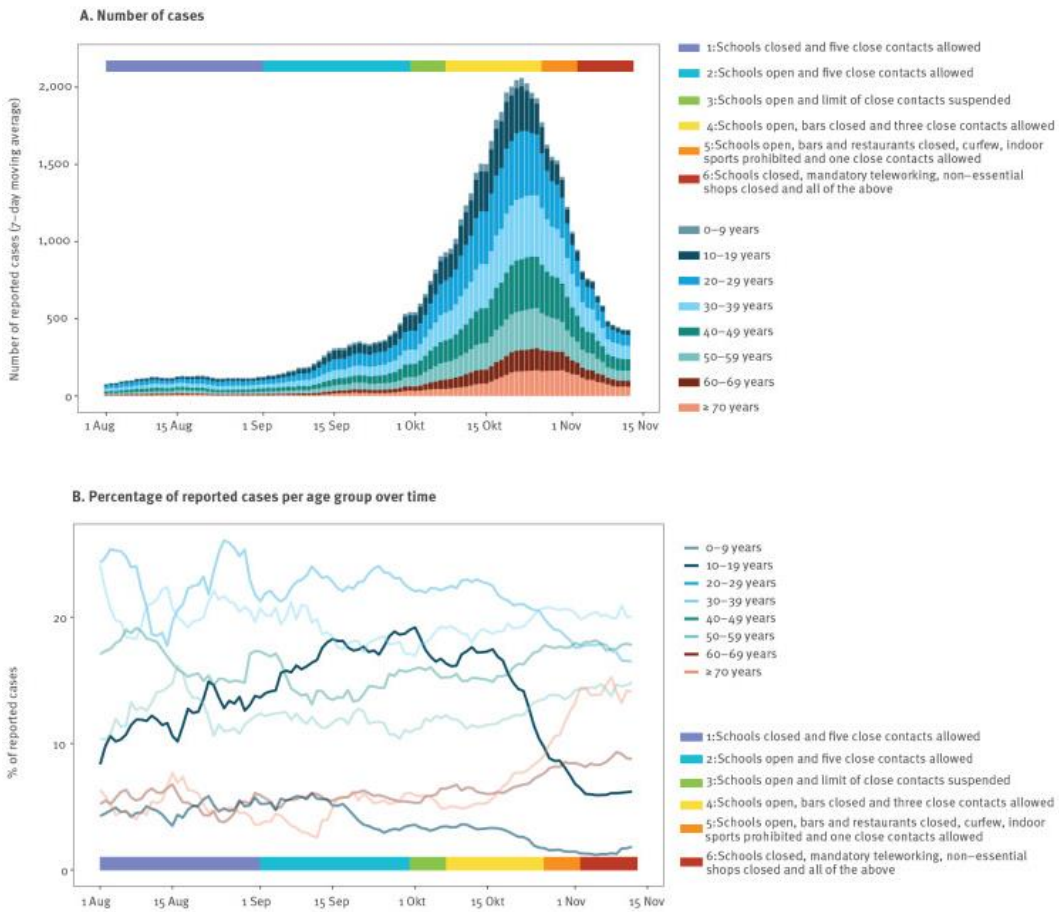

Figure 1. 7-day moving average of SARS-CoV-2 confirmed cases reported, Brussels region, 1 August–12 November 2020 (n = 415,412)

Effect of physical distancing measures on the number of reported contacts of cases

We compared differences in the mean weekly number of contacts reported per case to the telephone- and field agent-based contact tracing system, and confidence intervals (CI), assuming normality, at the start and end of each intervention period (Table). Following school reopening on 1 September, the mean number of reported contacts per case increased from 2.01 (95% CI: 1.73–2.29) in the last week of August to 2.83 (95% CI: 2.59–3.06) in the first week of September and further increased to 3.04 (95% CI: 2.93–3.15) by 30 September when the limit on the number of close contacts was suspended (Figure 2). A restriction to three close contacts and closure of bars on 6 and 8 October resulted in a gradual decrease in reported contacts per case from a mean of 2.81 (95% CI: 2.74–2.89) in the first week to 2.21 (95% CI: 2.16–2.25) 2 weeks later, just before contacts were further limited on 26 October. Following a limit to one close contact and closure of restaurants and sports facilities, the number of contacts per case further decreased to 1.94 (95% CI: 1.90–1.99), a 36.2% decrease compared with 30 September. When also shops were closed, teleworking became mandatory and schools started the autumn break, the mean number of reported contacts stagnated at 1.85 (95% CI: 1.78–1.91).

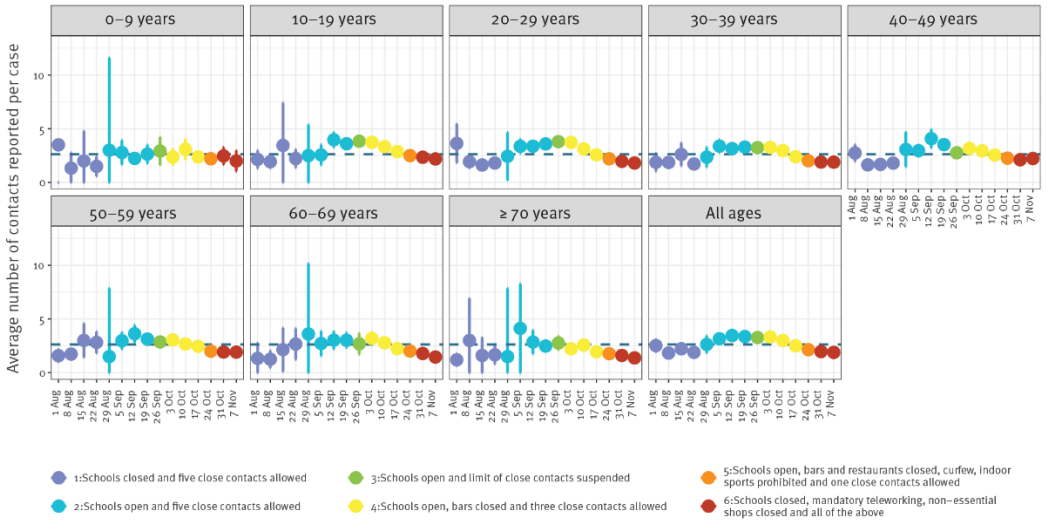

Figure 2. Weekly mean number of contacts reported per SARS-CoV-2 case (excluding cases not reporting any contacts), by age group, Brussels region, 1 August–12 November 2020 (n = 24,166). Weeks follow 7-day intervals from 1 August. Vertical bars indicate 95% confidence intervals. Colours indicate ongoing interventions or the intervention started that week. For trends in daily estimates and exact timing, see Supplementary Figure S2. For readability, the wide confidence intervals of the observation of the first week in the age group 0–9 years were removed. Of note, testing and related contact tracing for 0–6-year-olds was restricted to symptomatic cases only during the period of study.

The number of reported contacts per case was highest among 10–19-year-olds during our study period (3.11; 95% CI: 3.01–3.21); adults 70 years and older reported the lowest number (2.05; 95% CI: 1.93–2.18). However, over time, changes in the number of contacts following changes in physical distancing measures were largely similar across age groups, with the exception of the 0–9-year-olds (no changes observed) and adults 70 and older (less pronounced, Figure 2). Of note, testing and related contact tracing for 0–6-year-olds was restricted to symptomatic cases only during the period of study.

Effect of the number of reported contacts per case on SARS-CoV-2 transmission

We derived the instantaneous reproduction number R_t , i.e. the mean number of secondary cases that would arise from a primary case on a given day, from the daily number of reported cases, assuming an uncertain serial interval distribution (i.e. drawn from multiple truncated normal distributions with mean 5.19 days, 95% credible interval (CrI): 4.37–6.02), setting a 7-day sliding window, and estimating CrI using bootstrapping [3]. The R_t peaked on 17 September at 1.48 (95% CrI: 1.35–1.63). Three weeks after the gradual restriction of close contacts (first three, then one) and the closure of bars, restaurants and sport facilities, R_t had decreased by 44.6% to 0.82 (95% CrI: 0.79–0.85) (Figure 3). Even though a change in testing strategy to symptomatic cases only might have contributed to the drop in R_t, the drop continued in the 2 weeks following the change.

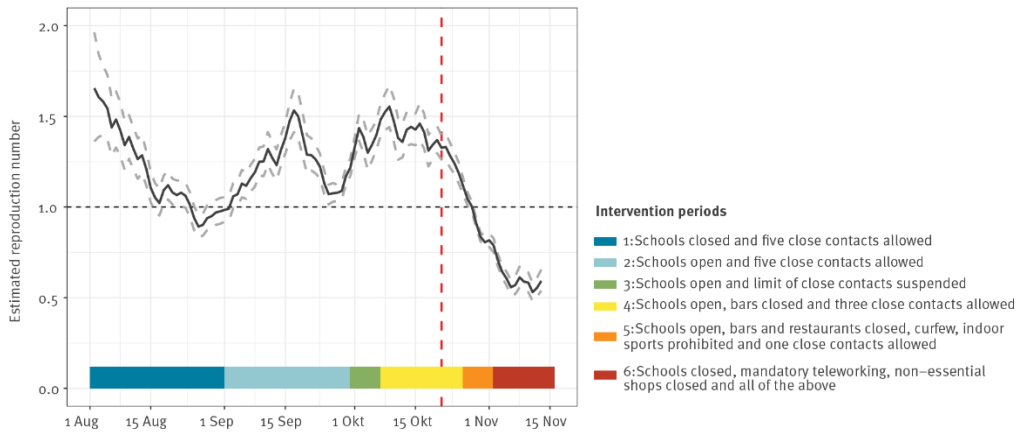

Figure 3. Estimated instantaneous reproduction number R_t based on daily reported cases and a mean 5.2-day serial interval (95% credible interval: 4.4–6.0 [14]), Brussels region, 1 August–12 November 2020 (n = 63,838). After 21 October (vertical dashed red line) asymptomatic contacts were excluded from SARS-CoV-2 testing. The dashed grey lines are 95% credible intervals. The horizontal dashed black line corresponds to a reproduction number of 1. The analysis was done using the EpiEstim R package [3].

Age-specific transmission patterns

Among 2,387 primary–secondary case pairs identified during the period 1 August to 30 November, transmission within the same age group was predominant (33.4%, 797/2,387). Infections originating from 10–19-year-olds were seldom recorded in August and November when schools were closed but testing of this group was low at these times as well (Figure 4A, Supplementary Figure S3). After schools reopened, transmission between all age groups became more apparent. In the month after reopening schools, 8.9% (67/755) of infections were from 10–19-year-olds to other age groups and 17.4% (131/755) from other age groups to 10–19-year-olds (Figure 4B). During extended autumn holidays and the closure of all non-essential services starting on 2 November (Figure 4D), intragenerational transmission was highest at 39.4% (63/160). Transmission within older age groups (≥ 50 years) became more frequent later in the second pandemic wave.

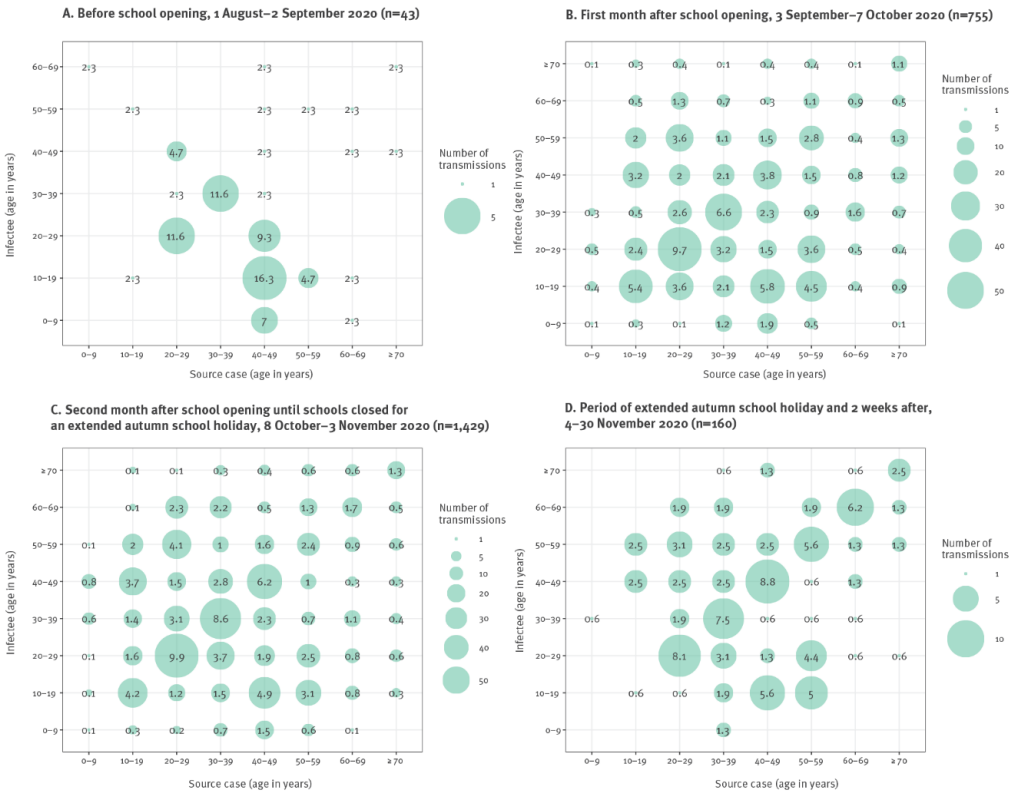

Figure 4. Transmission matrix between primary and secondary cases of all identified transmission events, 1 August–30 November 2020 (n = 2,387)

Age-specific trends in reported SARS-CoV-2 cases

SARS-CoV-2 case reports among 10–19-year-olds increased throughout August and September (Figure 1B), coinciding with an increasing testing rate in this age group (spearman rank correlation coefficient = 0.74; p value < 0.001; Supplementary Figure S2). At the time schools reopened (1 September), we did not observe any significant change in the proportion of 10–19-year-olds among all diagnosed cases (adjusted for 4 days reporting delay; Poisson regression risk ratio 1.23; 95% CI: 0.79–1.94; Supplementary Figure S5). When asymptomatic contacts were excluded from SARS-CoV-2 testing (from 21 October onwards), the proportion of 10–19-year-olds fell from 16.9% of cases (3,478/20,535 during the 2 weeks preceding the change) to 9.9% (2,214/22,330 during the 2 weeks following the change, Figure 1B). The proportion of adults 70 years or older who tested positive increased from 5.2% (727/13,872) during the first 2 weeks of October to 13.8% (1,574/11,430) in the first 2 weeks of November (Figure 1B).

Ethical statement

The study was approved by the Institutional Review Board of the Institute of Tropical Medicine (reference number 1423/20) and the Ethics committee of the Antwerp University Hospital (reference number 20/34/435).

Discussion

September 2020 saw a persistent increase in SARS-CoV-2 cases in the Brussels region following increased social mixing across all ages, as inferred from trends in the number of reported contacts per case. Stringent physical distancing measures were introduced 1 month after a persistent increase in R_t. These initial measures (a limit to three close contacts per person, a curfew, closure of bars and recommended teleworking) reduced reported contacts of cases by more than a third within 3 weeks,

resulting in an $R_t < 1$ by 29 October; they reduced social mixing sufficiently to control transmission, even with high case numbers and without closing schools or full lockdown.

In contrast to the first pandemic wave, primary and secondary schools remained open throughout the second wave. There is general consensus that children attending primary school contribute little to transmission [4]. In contrast, the role of teenagers and secondary schools is still much debated. Teenagers can transmit and show a viral load comparable to adults [5]. Nonetheless, several studies indicated either lower susceptibility or a higher proportion of asymptomatic individuals among teenagers which might result in fewer secondary infections originating from younger individuals [4,6-8]. Modelling studies investigating the role of secondary schools have shown that school closures can help alter transmission dynamics – albeit insufficiently for control and based on data from the first months of the pandemic with limited preventive measures in schools [e.g. 7,9,10]. Our findings confirm transmission among and from teenagers, with intergenerational transmission apparent following school opening. Nonetheless, their relative role was limited: transmission events from 10–19-year-olds to other age groups remained fewer than those from adults, and the proportion of cases among 10–19-year-olds did not significantly change after school reopening. After school reopening, the number of reported contacts per case increased across all age groups, suggesting a change in behaviour and mobility of all age groups, which may, at least in part, indirectly relate to school opening, and resulting in transmission particularly within the individual age groups, and an increased R_t.

Epidemic growth among older adults was delayed when compared to that in younger age groups, similar to observations in other European countries. Transmission of SARS-CoV-2 varies between age groups and settings [11]. In a socially structured disease system, transmission of infectious agents among individuals with social networks less linked to the general population (e.g. nursing home residents) can increase disproportionately when a network-specific abundance threshold, which may be different from the conventional $R > 1$ for the spread of infections, is reached [12]. We hypothesise that this so-called percolation phenomenon may explain why transmission among older adults peaked later.

Our study had some limitations. Firstly, the number of reported contacts per case was smaller (mean in August: 2.0; 95% CI: 1.8–2.0) and less heterogenous than what participants in a Belgian contact survey reported (mean: 3.5 during the period 27 July to 10 August) [13]. This was probably a result of our analyses only considering high-risk contacts (physical or cumulative 15 min non-physical contact within 1.5 m) and a result of poor recall of context-specific accidental social contacts (e.g. public transport, bars) or reluctance to report contacts. Yet, age-specific differences were comparable, suggesting that the conclusions based on trends over time remain valid. Secondly, only a small proportion of cases were known contacts, indicating high volumes of undetected transmission or poor linking between data. Thirdly, a shift in testing policy to include only symptomatic cases from 21 October onwards is likely to have resulted in fewer identified transmission events involving children or teenagers because these groups more frequently present without or with mild symptoms. This shift in testing could have resulted in an underestimation of R_t at the end of October. However, R_t continued to decrease steadily after the change in testing strategy, suggesting that a true drop in transmission levels is likely. To determine a causal relationship between measures implemented and social mixing, in turn affecting SARS-CoV-2 transmission, we made sure we observed a strong correlation, coherence between the different analyses in the study, that no other change in policy or context could explain the effect observed, that the observed effect followed the introduction of a measure, and that there was a dose–response relationship such as

between the number of contacts and *Rt*. Moreover, our findings are plausible, and are consistent with prior modelling and real-world studies on COVID-19 and other infectious agents.

Conclusion

The second pandemic wave in Brussels was a result of increased social mixing across all ages in the absence of strict physical distancing measures. Limiting the number of close contacts per person and closure of bars and restaurants resulted in a rapid decrease in reported contacts of cases, sufficient to control SARS-CoV-2 transmission (lowering R_t to < 1).

Acknowledgements

We thank the Common Community Commission for reaching out to collaborate and providing insight at several stages of the study, and David Hercot for helpful last-minute discussions. We thank the contact tracing team for data collection, and Sciensano for making age-specific case reports and testing data open access.

Funding: This study was partially funded by EU grant 874850 MOOD and is catalogued as MOOD [004]. The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of the European Commission.

Conflict of interest: None declared.

Authors' contributions

BI and EvK conceptualised the design and analyses and wrote the draft manuscript; LP contributed to the data analysis and interpretation; IN supported the interpretation of results and revised the manuscript; IH did the data curation and revised the manuscript; ML revised the manuscript; MvdS contributed to the interpretation and revised the manuscript

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Supplementary material

Processing of contact tracing and case report data

In May 2020, Belgium implemented a phone- and field agent-based contact tracing system. SARS-CoV-2 PCR-positive cases were phoned or visited, and asked to report who they had contact with, recording names and postal codes of high-risk contacts. High-risk (close) contacts, defined as persons with whom the SARS-CoV-2 PCR-positive case had physical or cumulative 15 minutes non-physical contact within 1.5m from 2 days before to 7 days after onset of symptoms of a confirmed SARS-CoV-2 case, were identified and recommended to undergo SARS-CoV-2 PCR testing, regardless of symptoms. For reported contacts aged 0-6 years, and from October 21 onwards across all ages, testing was restricted to symptomatic individuals only[2]. In primary schools, pupils and teachers in the same class of a confirmed case were considered low-risk contacts, therefore did not require testing, except if presenting symptoms. In secondary schools, the regular high-risk contact definition and testing criteria were applied.

To identify transmission events between primary (index) and secondary cases (contacts that tested SARS-CoV-2 positive within 3 weeks after the reported date of contact with the index case), we linked pseudonymised data on reported high-risk contacts generated by the contact tracing system with SARS-CoV-2 case data (including age) using a unique identifier based on first and last name. Homonyms that resulted in duplicates with the same unique identifier were excluded from the dataset.

We used 3 datasets from the Brussels region: (i) contacts reported by reported cases through contact tracing: date and index case ID; (ii) daily reported cases numbers; (iii) the primary-secondary case transmission events. We described case numbers, testing rates, test positivity, and mean numbers of high-risk contacts reported per SARS-CoV-2 case, by age group. We built a linear regression model to evaluate trends in the daily mean number of reported contacts by intervention period. We estimated the instantaneous reproduction number (Rt) from daily reported cases and analysed its correlation to the number of reported contacts. We described age patterns of identified transmission events in a matrix linking index and secondary cases. Data processing and analysis scripts are accessible on a GitHub repository: https://github.com/ingelbeen/covid19bxl.

A total of 52,484 cases were referred for contact tracing. Among these cases, 24,166 (46.0%) reported at least one contact, 61,754 in total. Matching operational case and contact databases resulted in a final 19,194 cases with recorded age and 51,177 contacts. The time between the last reported contact and contact tracing was median 2 days (interquartile range 0-5 days). Until 30 November, we traced back 2,443 reported contacts that tested SARS-CoV-2 positive within 3 weeks, yielding primary-secondary case pairs, 2,387 with age recorded.

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Description of regression models

To visualise and describe changes in contact patterns over time, we fitted a segmented linear regression allowing for step and slope changes between distinct intervention periods as follows:

$$Y_t = \beta_0 + \beta_1 T_{t-2} + \beta_{2_i} X_t + \beta_{3_i} X_t T_{t-2} + \epsilon_t \qquad (1)$$

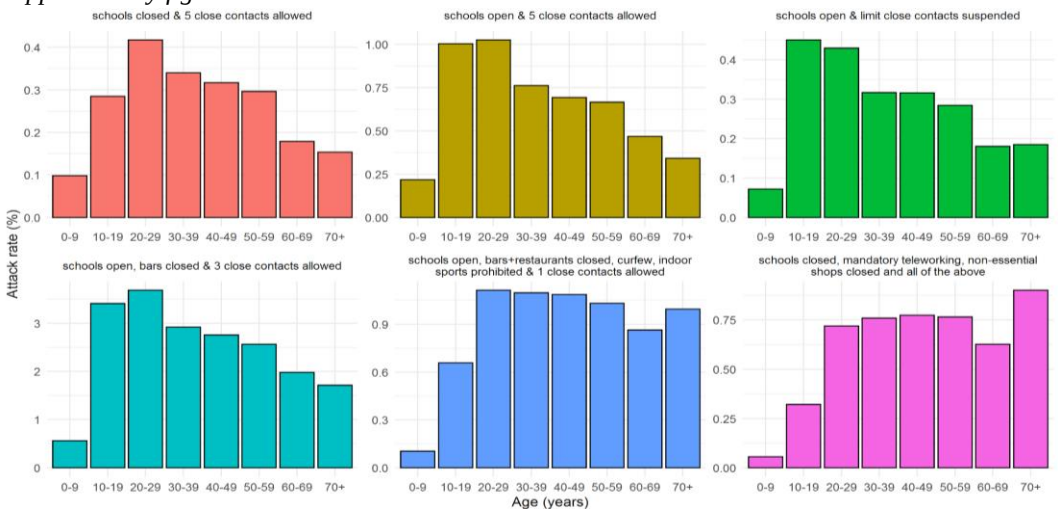
Where Y_t is the expected mean number of contacts (individuals) on day t. T_t represents the day starting August 1, thus β_1 can be interpreted as the underlying trend in contact patterns without any changes in interventions. X_t represents a dummy variable indexing the 6 distinct intervention periods i, with β_2 and β_3 representing the step and slope change in contacts following the introduction of interventions. We added a 2-day lag for delay between the moment of the at risk contact with the case and reporting and identifying of that contact by the case, based on the median number of days between the last reported contact and when the concerned contact person was traced.

We describe changes in the proportion of daily reported cases ($I_{t_{10-19}}$) among teenagers in the months pre- and post-school opening (August to September), using Poisson regression with a log-link and offset term representing the total daily reported cases.

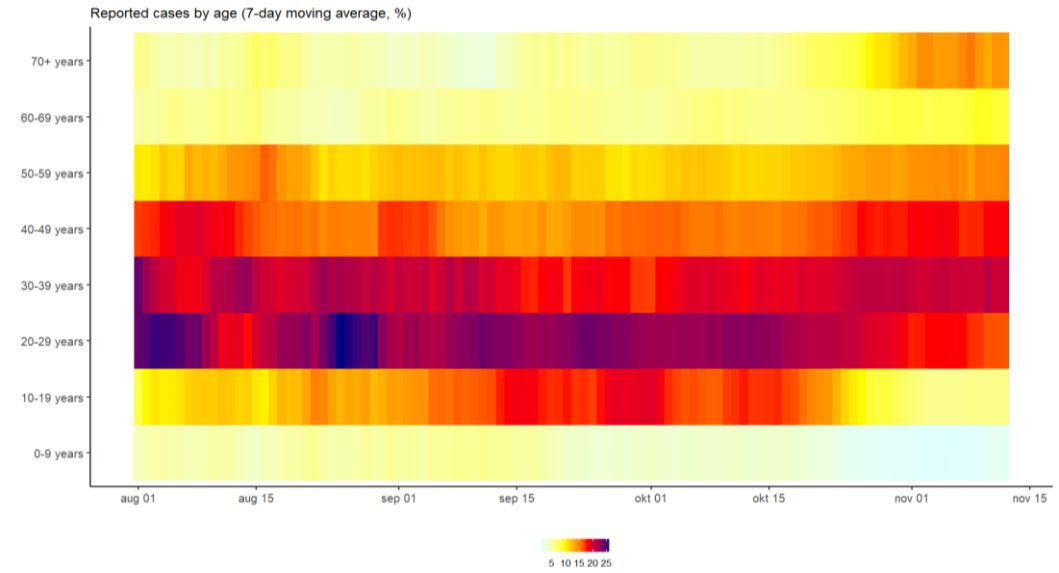
$$\log\left(I_{t_{10-19}}\right) \sim \log\left(I_{t_{total}}\right) + \beta_0 + \beta_2 T_{t-4} + \beta_3 X_t + \beta_4 X_t T_{t-4} + \beta_5 X_{test_{10-19}} + \beta_6 X_{weekend} \qquad (2)$$

T_t represents the days from August until September, capturing the underlying trend pre-school opening, X_t represents a dummy variable indexing 0 and 1 before and after school opening respectively. We adjusted the periods for reporting delays by including a lag between exposure and case report (4 days). The daily number of tests performed among teenagers was accounted for and depicted by $X_{test_{10-19}}$ as well as whether the case was reported positive during the weekend $X_{weekend}$. We compared model fits using Akaike Information Criterion (AIC), assuming different time trends following school opening (i.e. no, vs a step vs a step and slope change). Models with and without adjustment for school provided similar fits (AICs of 364.9, 363.1, and 362.4 for a model with a step and slope change, a step change only and no change at all respectively). Of note, models with and without testing showed similar fits, while $X_{test_{10-19}}$ proved highly correlated with time.

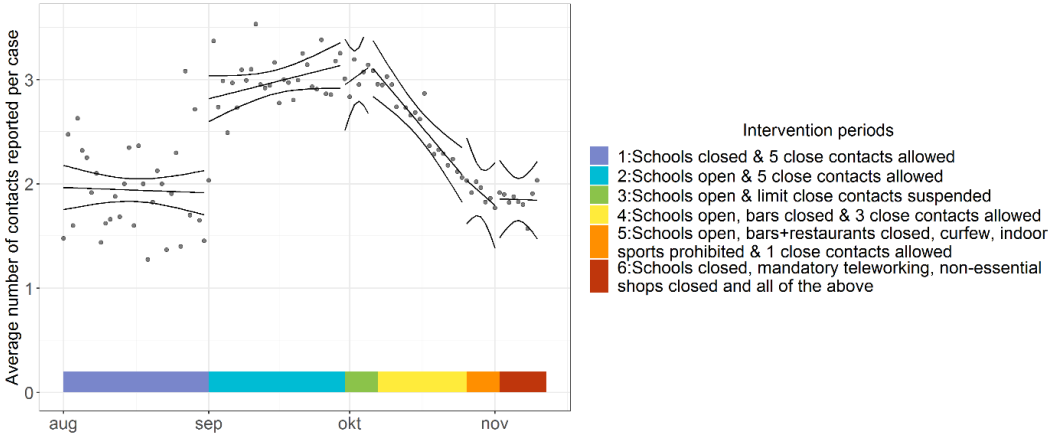
Supplementary figures



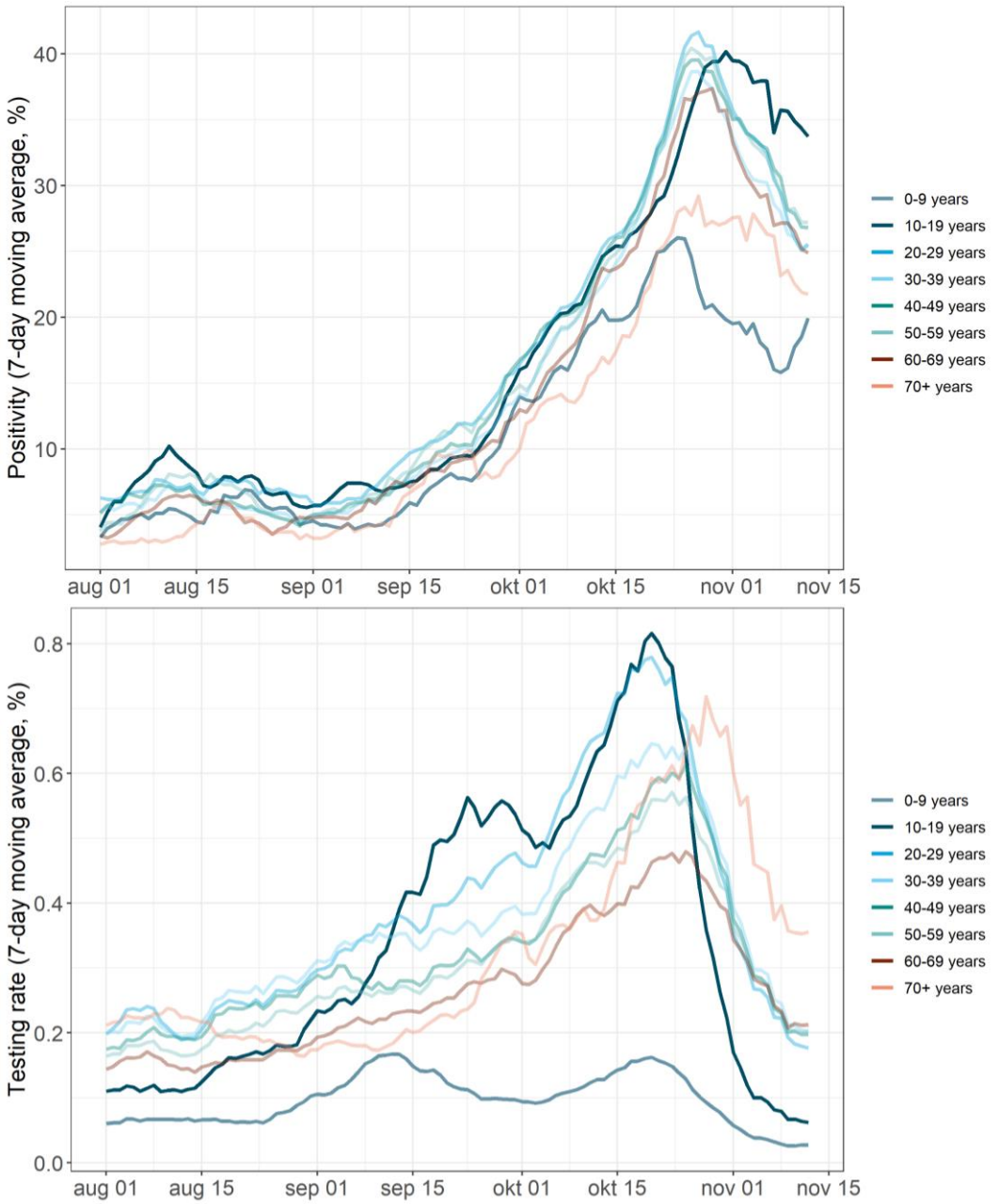
Supp Fig 1A. Percentage of the population which was SARS-CoV-2 confirmed by age group and by period of physical distancing measures. Source population numbers: https://statbel.fgov.be/en/themes/population/structure-population



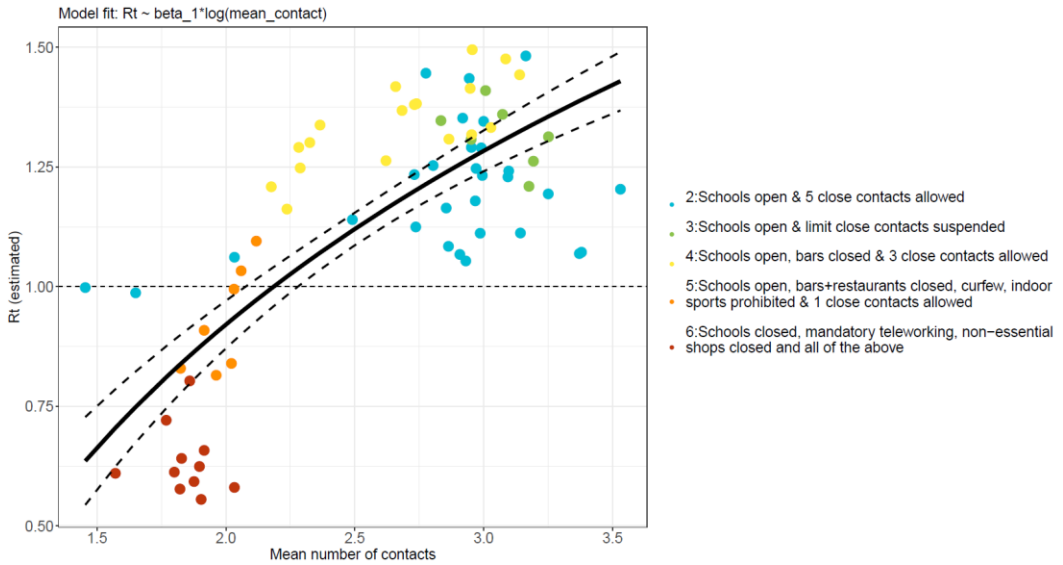
Supp Fig 1B. Percentage of the population which was SARS-CoV-2 confirmed by age group and by period of physical distancing measures. Source population numbers: https://statbel.fgov.be/en/themes/population/structure-population



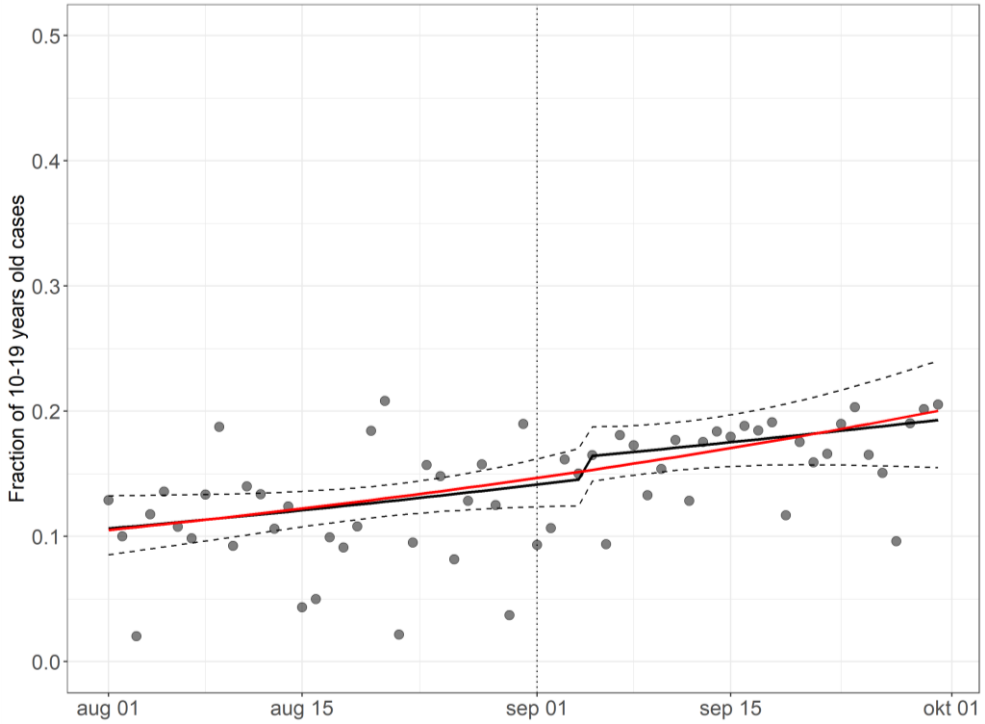
Supp Fig 2. Daily average number of contacts reported per SARS-CoV-2 case (excluding cases not reporting any contacts) with fitted estimated linear trends and 95% confidence intervals, using segmented linear regression with an interaction term for date and intervention periods, allowing for a step change. Lines are plotted as discontinuous for readability. The start of each segment in the linear regression is corrected for the median two days between the last reported contact and the interview.



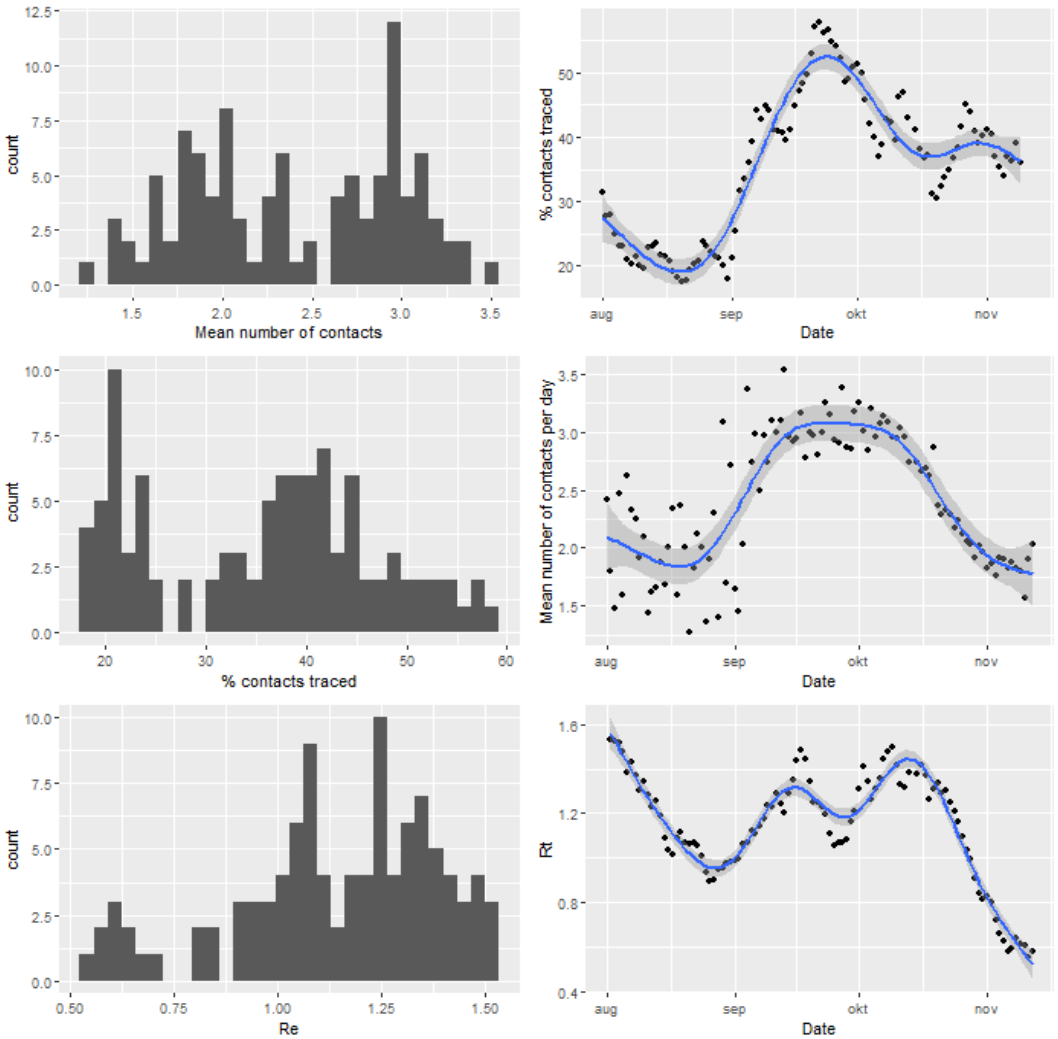
Supp Fig 3. Percentage of positive SARS-CoV-2 tests (A) and testing rate (B) by age group in the Brussels region. Source data: Sciensano and https://statbel.fgov.be/en/themes/population/structure-population



Supp Fig 4. Relationship between the number of reported contacts and reproduction number. Fitted linear regression model, regressing the instantaneous reproduction number (Rt) over the log daily mean number of contacts. August 2020 was excluded given the large variance we observed on the daily number of reported contacts.



Supp Fig 5. Model fit of the fraction of 10-19 years olds among SARS-CoV-2 cases in Brussels before and after school opening, corrected for a 4-day test and report delay. Dotted line represents the timing of school opening. Red = model fit of a model assuming no step and slope change after school opening, setting variables representing weekend reporting to 0 (weekday) and number of tests among teenagers at its mean value. Black = model fit and 95% confidence interval of a model allowing for a step and slope change after school opening.



Supp Fig 6: Frequency distributions of the mean number of contacts reported, the percentage of reported contacts who could be successfully traced and the instantaneous reproduction number (Rt).

Page 67: Informal medicine vendor, Nanoro, Burkina Faso, January 2023. Photo by Brecht Ingelbeen

6- Comparative assessment of the prevalence, practices and factors associated with self-medication with antibiotics in Africa

Published 03 May 2021 in Tropical Medicine and International Health, doi:10.1111/tmi.13600

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Abstract

Objective To evaluate and compare the prevalence, reasons, sources and factors associated with selfmedication with antibiotics (SMA) within Africa.

Methods Systematic review and meta-analysis. An electronic search of PubMed and databases was performed for observational studies conducted between January 2005 and February 2020. Two reviewers independently screened abstracts and full texts using the PRISMA flowchart and performed quality assessment of eligible studies. Both qualitative and quantitative syntheses were carried out.

Results Forty studies from 19 countries were eligible for qualitative synthesis. The prevalence of SMA in Africa ranged from 12.1% to 93.9% with a median prevalence of 55.7% (IQR 41–75%). Western Africa was the sub-region with the highest reported prevalence of 70.1% (IQR 48.3–82.1%), followed by Northern Africa with 48.1% (IQR 41.1–64.3%). We identified 27 antibiotics used for self-medication from 13 different antibiotic classes. Most frequently used antibiotics were penicillins (31 studies), tetracyclines (25 studies) and fluoroquinolones (23 studies). 41% of these antibiotics belong to the WHO Watch Group. The most frequent indications for SMA were upper respiratory tract infections (27 studies), gastrointestinal tract symptoms (25 studies) and febrile illnesses (18 studies). Common sources of antibiotics used for selfmedication were community pharmacies (31 studies), family/friends (20 studies), leftover antibiotics (19 studies) and patent medicine stores (18 studies). The most frequently reported factor associated with SMA was no education/low educational status (nine studies).

Conclusions The prevalence of SMA is high in Africa and varies across sub-regions with the highest prevalence reported in Western Africa. Drivers of SMA are complex, comprising of socioeconomic factors and insufficient access to health care coupled with poorly implemented policies regulating antibiotic sales.

Introduction

Self-medication is defined by WHO as treatment of self-recognised disorders or symptoms by use of medicines without prior consultation by a qualified health professional or intermittent/continued use of medicines previously prescribed by a physician for chronic/recurring diseases [1]. When properly practised, self-medication can provide some benefits to individuals and health systems: It saves time spent queuing up for medical consultations, saves scarce medical resources from being used on minor conditions, lightens the workload of doctors, decreases health care cost and reduces absenteeism from work [2-4]. Despite these potential benefits obtained from practising self-medication, there are many undesired outcomes that may result from inappropriate self-medication use, especially with antibiotics [5]. WHO defines inappropriate antibiotic use as the use of antibiotics without proper indication, or administering wrong dosages, incorrect treatment duration, late or

absent downscaling of treatment, poor adherence to treatment, and use of poor quality or substandard antibiotics [6]. Self-medication with antibiotics (SMA) contributes to accelerating the emergence and spread of antimicrobial resistance (AMR) [1, 7, 8]. In Low and Middle-Income Countries (LMIC), it is estimated that about 80% of antibiotics are used outside official healthcare facilities, of which about 20–50% are used inappropriately [9]. Other negative outcomes related to self-medication include wastage of economic resources from prolonged treatment duration due to incorrect management of infections, delayed or wrong diagnoses, drug interaction and adverse reactions [10]. The increasing practice of self-medication, especially with antibiotics in Africa, warrants sensitisation of the general public and health professionals to avoid inappropriate use [2]. Whilst various studies have been conducted on SMA in different countries in Africa, there has not yet been a systematic review that comprehensively assesses SMA in the entire region. Patterns of self-medication vary among different populations and regions and are influenced by many factors [2, 5]. The type of antibiotics used for SMA, the extent of SMA and the reasons for it may also vary from country to country especially in Africa [2]. Socio-economic factors such as low income/high rate of unemployment and low level of education, poor access to health care, informal access to antibiotics, storage of antibiotics at home and health-seeking behaviours of the general population have been reported in other studies from Asia, the Middle East and South Eastern Europe [4, 5, 11]. These factors have not yet been well-documented in the African context [5]. Antibiotic use, and in particular inappropriate use, is a major driver of the silent and growing AMR pandemic, also in Africa. Nevertheless, most African countries have not yet given priority to control this threat, with the majority of these countries lacking AMR preparedness activities (i.e. national action plans for AMR control, comprehensive national AMR policies, targeted capacity building activities, regulatory measures on circulation of substandard or counterfeit antimicrobials and AMR surveillance strategies) [12-14]. Africa has been harder hit by the growing AMR pandemic compared to other regions [15, 16]: it carries a high burden of infectious diseases which compounds the growing weight of non-prescription sales and inappropriate use of View PDF antibiotics, and thus, also the aforementioned challenges that notably accelerate AMR [17]. It was estimated in 2011 that more than half of the antibiotics used in communities especially in Africa are sold without a medical prescription [18]. Contextual evidence of practices and drivers related to AMR and SMA in Africa are required to guide policy development, action plans and control programmes [5, 14]. This review aimed to evaluate the magnitude and drivers of SMA in Africa and to generate evidence-based recommendations to control and reduce SMA and contain the rising challenge of AMR in Africa.

Methods

Search strategy

Table 1. Search strategy

Database	Search mode	Search term syntax
Medline via PubMed	All fields	"Anti-Infective Agents "[Mesh] AND ("Self Medication"[Mesh] OR "Nonprescription Drugs"[Mesh]) OR "Drug Misuse"[Mesh]) AND "Africa"[Mesh]
	Articles	(antimicrobial* OR antibacterial* OR antibiotic*) AND (“self medication” OR self-medication OR “non prescription” OR non-prescription OR “over-the-counter OR “inappropriate") AND (determinants OR “associated factors”) -Asia -Europe -America -Review

An electronic systematic search of the Medline through PubMed and databases was performed in line with the PRISMA statement [19]. Search terms and keywords were identified through a pilot literature search and Boolean operators were used to combine these terms to come up with a search

strategy (Table 1). Medical Subject Headings (MeSH) were used to synchronise synonymous terms in PubMed. We excluded reviews, animal models, editorials, letters, opinions or comment publication types. To ensure that no similar review had been registered or previously carried out, a preliminary scoping search was done on the following registries: International Prospective Register of Systematic Reviews (PROSPERO), International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY), Research Registry and Cochrane Library of Systematic Reviews and also on the PubMed and databases.

Selection of articles for review

Articles included in this review were selected using the PRISMA Flow Diagram [20]. Two reviewers EVY and JNF, independently screened studies against the eligibility criteria and discrepancies were resolved through a third reviewer BI. Titles and abstracts of all records identified through database searches were screened for duplicates and studies that met the inclusion criteria selected (i.e. cross-sectional studies and mixed methods studies (cross-sectional surveys with qualitative work) carried out on SMA in Africa between January 2005 and February 2020). Studies on SMA conducted in other regions, dissertations on SMA, studies on general self-medication, studies on non-prescription antibiotic sales and studies on antimalarials were excluded. Additional articles that met the inclusion criteria were identified through reference mining. The full text of studies selected for qualitative analysis was reviewed and studies with no relevant data, qualitative studies, and studies of which full text could not be retrieved were excluded.

Assessment of the quality of included studies

The quality of studies selected for full-text review was appraised using the 'risk of bias in prevalence studies evaluation' tool by Hoy et al. [21], appraising the studies on nine criteria.

Data extraction

Titles and abstracts of studies retrieved were saved in Mendeley. The following characteristics were extracted using a spreadsheet in Excel: country, corresponding author, year of publication, study site, study design, sampling strategy, recall period, sample size and response rate. The prevalence of SMA, type of antibiotics used for self-medication, reasons for practising SMA, sources of antibiotics, and factors associated with SMA were also extracted.

Data syntheses

Both qualitative and quantitative syntheses were performed. In the qualitative synthesis, we analysed and summarised descriptive variables and outcomes of interest (prevalence, reasons for SMA, sources of SMA, factors associated with SMA and common antibiotics used for SMA). We used the WHO AWaRe Classification [22] to group antibiotics used for self-medication. Reasons for SMA were analysed using the modified conceptual framework of access to health care [23]. Prevalence estimates were summarised using medians and interquartile ranges. Quantitative synthesis was conducted only on household studies because these are most representative for SMA among the general population, unlike studies limited to university students (frequently (para)medical students), or to hospital patients. Meta-analysis was done using the 'metafor' package in R software (version 3.6.1). A random-effect model was used to calculate the weight of each study and the Freeman-Tukey double arcsine transformation was used to stabilise the variance in the proportions of individual studies. Heterogeneity was checked by Cochran's Q-test and quantified by the I . Heterogeneity was considered present and statistically significant when I > 50% and P-value <0.05. Findings were displayed graphically using a forest plot. To verify publication bias, a funnel plot was constructed using Double Arcsine transformed proportions.

Results

Search results

The databases were searched on February 26 , 2020 and a total of 5291 citations were identified: 171 through PubMed and 5120 through . 164 duplicate citations were discarded. The titles and abstracts of the remaining 5127 studies were screened and 5080 records were disqualified as they did not meet the inclusion criteria. References in the selected 47 studies were searched and another eight studies identified, rendering 55 studies for full-text review. After reviewing the full text of the selected studies, 15 studies were excluded. The remaining 40 studies underwent qualitative synthesis. Of those, 15 studies were selected for quantitative synthesis (Figure 1).

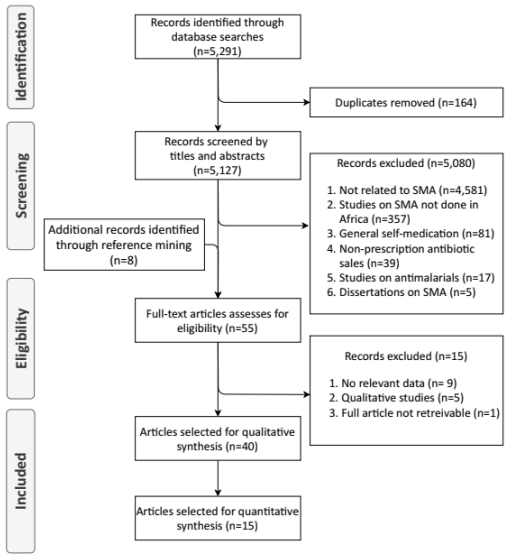

Figure 1: PRISMA Flowchart

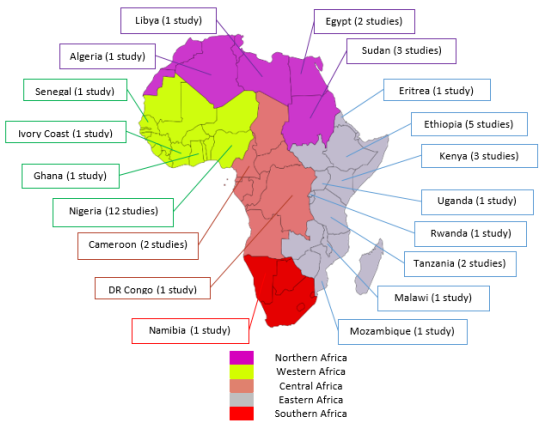

Figure 2. Distribution of selected studies by countries and sub-regions

The 40 studies included in this review were from 19 African countries and from all five African sub-regions: 7 from Northern Africa (24–30), 3 from Central Africa (31–33), 14 from Western Africa (34,35,44–47,36–43), 15 from Eastern Africa (48,49,58–61,50–57) and 1 from Southern Africa (62) [Figure 2]. Thirty-seven of these studies were cross-sectional surveys and 3 mixed methods (i.e. cross-sectional surveys with qualitative work) (47,53,60). Fifteen of these studies were carried out in households, 13 studies academic settings (universities), 4 studies in pharmacies, 3 studies in health facilities, and 5 studies in other settings (markets, streets, shopping malls, offices). All studies together included 21,358 participants with sample sizes ranging from 110 - 1750. The recall period used in data collection ranged from 3 days to 10 months, reported by 32 studies [Table 2].

Table 2: Study characteristics and prevalence rates of SMA

Reference	Country	Study site	Study participants	Sampling method	Sample size	Recall period/ weeks	Response rate (%)	Prevalence of SMA (%)	95% CI
Gacem et al, 2015 (85)	Algeria	Pharmacies	General public	Simple random	159	2	NR	12.6	07.4 - 17.8
Elden et al, 2020 (86)	Egypt	Universities	Students	Multistage	600	40	94	77.7	74.4 - 81.0
El-Hawy et al, 2017 (87)	Egypt	Clubs, cafes, streets	General public	Convenient	400	8	89.7	64.3	59.6 - 69.0
Ghaieth et al, 2015 (88)	Libya	Universities	Students	NR	665	16	55	46	42.2 - 49.8
Awad et al, 2005 (89)	Sudan	Households	General public	Multistage stratified cluster, simple random	1750	NR	89.7	48.1	45.8 - 50.4
Awad et al, 2007 (90)	Sudan	Universities	Undergraduate students	Multistage stratified cluster, systematic random	1121	24	86.2	55	52.1 - 57.9
Ahmed et al, 2014 (91)	Sudan	Households	General public	Simple random	442	36	NR	41	36.4 - 45.6
Ngu et al, 2018 (92)	Cameroon	Hospitals	Patients with respiratory tract infection	Convenient	308	24	NR	41.9	36.4 - 47.4
Amin et al, 2019 (93)	Cameroon	Health facilities	Patients	NR	329	16	NR	68.4	63.4 - 73.4
Bunduki et al, 2017 (94)	DR Congo	Universities	Students	Convenient	500	3	86	90.7	88.2 - 93.2
Donkor et al, 2012 (95)	Ghana	Universities	Students	Stratified sampling, Convenient	600	32	90	70	66.3 - 73.7
Olayemi et al, 2010 (96)	Nigeria	Universities	Undergraduate students	Simple random	430	NR	65.8	56.9	52.2 - 61.6
Abdulraheem et al, 2016 (97)	Nigeria	Health Centres	All patients	Simple random	1150	24	93.9	82.2	80.0 - 84.4
Badger-Emeka et al, 2018 (98)	Nigeria	Households	General public	Convenient	400	28	NR	86	83.2 - 89.8
Ehigiator et al, 2010 (99)	Nigeria	Universities	Dental students	NR	208	12	96.2	53.5	46.5 - 60.3
Israel et al, 2015 (100)	Nigeria	Ministries, departments, units	Civil servants	Simple random	526	NR	89.5	93.9	91.9 - 95.9
Fadare et al, 2011 (101)	Nigeria	Universities	Medical students	Convenient	183	4	83.2	38.8	31.7 - 45.9
Sapkota et al, 2010 (102)	Nigeria	Universities	Students	Three-stage cluster, simple random	740	NR	95.4	24	20.9 - 27.1
Umar et al, 2018 (103)	Nigeria	Universities	Paramedical students	Stratified	115	NR	82	81.9	74.9 - 88.9
Yusuf et al, 2019 (104)	Nigeria	Households	General public	Simple random	300	8	85.3	70.3	65.1 - 75.5
Ajibola et al, 2018 (105)	Nigeria	Hall of residence	Community residents & undergraduate students	Convenient	1450	8	84.8	43	40.5 - 45.5
Khalid et al, 2019 (106)	Nigeria	Universities	Pharmacy students	Purposive	217	4	100	92.2	88.6 - 95.8
Bassoum et al, 2019 (107)	Senegal	Bus station	General public	Convenient	400	4	100	75	70.8 - 79.2
Hounsa et al, 2010 (108)	Ivory Coast	Pharmacies	General public	Simple random	1123	24	NR	59.7	56.8 - 62.6

Ateshim et al, 2019 (109)	Eritrea	Households	General public	Two-stage cluster, systematic random	580	12	99.5	45.1	41.1 - 49.1
Bogale et al, 2019 (110)	Ethiopia	Households	General public	Multistage, systematic random	605	12	98.3	67.3	63.6 – 71.0
Erku et al, 2017 (111)	Ethiopia	Households	General public	Multistage, stratified random, systematic random	720	8	90.3	63.5	60.0 – 67.0
Eticha et al, 2014 (112)	Ethiopia	Universities	Undergraduate Students	Stratified, simple random	422	4	96.4	44.5	39.8 - 49.2
Nyambega et al, 2017 (113)	Kenya	Markets, shopping malls and households	General public	Simple random	385	8	78	60	55.1 - 64.9
Owour et al, 2015 (114)	Kenya	Households	General public	Cluster, systematic random	350	3/7	NR	76.9	72.5 - 81.3
Sambakunsi et al, 2019 (115)	Malawi	Households	General public	Weighted cluster random, snowballing	110	NR	95.5	41	31.8 - 50.2
Tuyishimire et al, 2019 (116)	Rwanda	Universities	Undergraduate students	Simple random	570	NR	NR	12.1	09.4 - 14.8
Horumpende et al, 2018 (117)	Tanzania	Households	General public	Systematic random	300	4	NR	58	52.4 - 63.6
Kajeguka et al, 2017 (118)	Tanzania	Households	General public	Simple random	300	12	NR	55.7	50.1 - 61.3
Ocan et al, 2014 (119)	Uganda	Households	General public	Multistage cluster, Simple random	892	8	99.1	75.7	72.9 - 78.5
Gebeyehu et al, 2015 (120)	Ethiopia	Households	General public	Systematic random	1082	8	98.3	18	15.7 - 20.3
Gebrekirstos et al, 2017 (121)	Ethiopia	Drug retail outlets	General public	Stratified, simple random	829	8	94	47.1	43.7 - 50.5
Owuor et al, 2019 (122)	Kenya	Households	General public	Two-stage cluster, systematic random	380	NR	83.2	20.9	16.8 – 25.0
Mate et al, 2019 (123)	Mozambique	Households	General public	Three-stage cluster, Random	1091	12	73.1	20.9	18.5 – 23.3
Pereko et al, 2015 (124)	Namibia	Pharmacies	General public	Simple random	600	16	74.3	15.47	12.6 - 18.4

CI, Confidence Interval, NR, Not Reported, SMA, self-medication with antibiotics

Quality assessment of included studies

Studies eligible for qualitative synthesis (40 studies) were assessed for risk of bias. Three of these studies met all nine quality criteria in the assessment tool [48, 63, 64]. Twenty-four studies showed a low risk of bias [25, 26, 28, 30, 32, 34, 36, 40, 42, 43, 45, 48-52, 54-56, 59-61, 63-65], 15 studies showed a moderate risk of bias [24, 27, 31, 35, 37-39, 41, 44, 46, 57, 58, 62, 66], and one study showed a high risk of bias [33].

Prevalence of SMA

The prevalence of SMA ranged from 12.1% to 93.9%. Twenty-three studies reported prevalence estimates above 50%, 13 above 70% and 3 above 90% (90.3% from the Democratic Republic of Congo, 93.9% and 92.2% from Nigeria). Prevalence estimates of less than 20% SMA were reported in four studies. The overall median prevalence was 55.7% (IQR: 41%, 75%). The median prevalence was 48.1% (IQR: 41.1, 64.3%) for Northern Africa, 70.1% (IQR: 48.3%, 82.1%) for Western Africa and 47.1% (IQR: 31%, 65.4%) for Eastern Africa. The prevalence in studies conducted in households ranged from 18% to 86% with a median prevalence of 48.1% (IQR: 41%, 73%). A meta-analysis of these studies revealed a pooled prevalence estimate of 51.5% (95% CI: 40.1%, 62.8%). The I^2 = 99.1% (P < 0.0001) was indicative of pronounced heterogeneity. This means that the variation across studies was higher than that observed by chance, hence the pooled proportion of SMA was incongruous. The summary of results is presented in a forest plot (Figure 3).

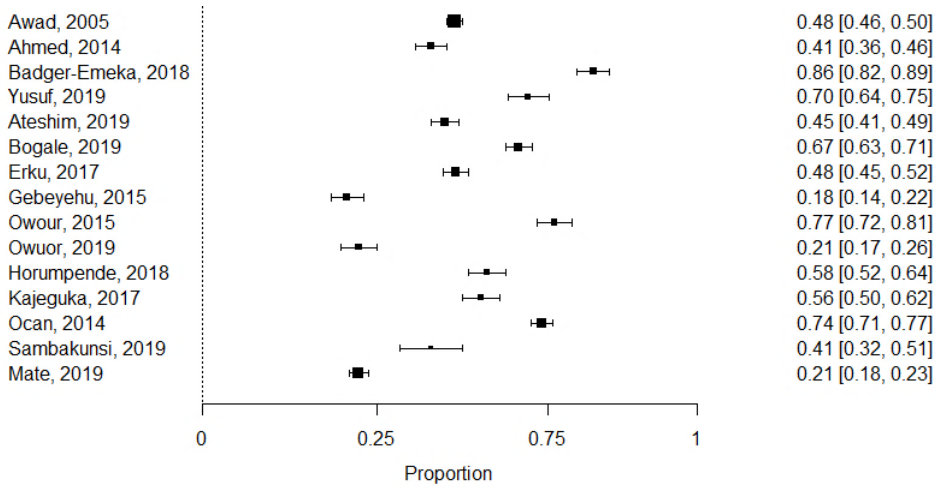

Figure 3. Forest Plot showing the proportion of SMA in household studies

We analysed the pooled estimates of the sub-regions exploring the cause of the observed heterogeneity. The pooled prevalence estimate was 44.5% (95% CI: 18.3%, 72.5%) for Northern Africa, 78.5% (95% CI: 51.4%, 96.4%) for Western Africa and 47.5% (95% CI: 35.4%, 59.8%) for Eastern Africa. High residual heterogeneity was equally observed with I2 = 98.8% (P < 0.0001) indicating that the observed heterogeneity was not due to sub-regions. Funnel plots showed an asymmetric distribution of studies with most of them falling out of the funnel indicative of publication bias (Figure 4).

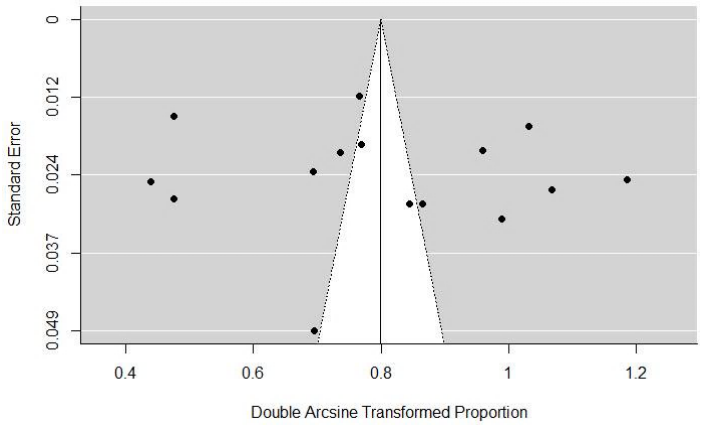

Figure 4. Funnel plot for household studies

Common antibiotics used in self-medication

Twenty-seven antibiotics from 13 classes were identified as used in self-medication and reported by 31 studies. The majority of these antibiotics (48%) belonged to the Access Group, 41% belonged to the Watch Group and only one antibiotic belonged to the Reserve Group [Table 3]. The most frequently used classes of antibiotics were penicillins (31 studies), tetracyclines (25 studies), fluoroquinolones (23 studies), imidazoles (19 studies), macrolides (10 studies), amphenicols (nine studies) and trimethoprim/sulphonamides (17 studies; Tables 3 and 4).

Table 3. AWaRe classification of antibiotics used for self-medication

Class of antibiotic	Antibiotic used in SMA	AWaRe Group
Penicillins (31 studies)	Amoxicillin	Access
	Cloxacillin	Access
	Flucloxacillin	Access
	Ampicillin	Access
	Penicillin	Access
	Ampicillin/Cloxacillin	Not recommended
	Amoxicillin/ clavulanic acid	Access
Fluoroquinolones (23 studies)	Ciprofloxacin	Watch
	Levofloxacin	Watch
	Ofloxacin	Watch
Trimethoprim/Sulphonamides (17 studies)	Cotrimoxazole	Access
Tetracyclines (25 studies)	Tetracycline	Access
	Doxycycline	Access
Macrolides (10 studies)	Erythromycin	Watch
	Azithromycin	Watch
Imidazoles (19 studies)	Metronidazole	Access
Amphenicols (9 studies)	Chloramphenicol	Access
Cephalosporins (4 studies)	Cefuroxime	Watch
	Ceftriaxone	Watch
	Cefixime	Watch
Aminoglycosides (3 studies)	Gentamycin	Access
	Streptomycin	Watch
Aminocyclitols (1 study)	Spectinomycin	Access
Nitrofurans (1 study)	Nitrofurantoin	Access
Glycopeptides (1 study)	Vancomycin	Watch
Polymyxins (1 study)	Polymyxin B	Reserve

SMA, Self-medication with antibiotics

Table 4. Common antibiotic classes used in self-medication and their sources

References	Country	Common classes of antibiotic and percentage used	Sources of antibiotics and percentage
Gacem et al, 2015 (85)	Algeria	Penicillins Tetracyclines Macrolides Imidazoles	NR
Ngu et al, 2018 (92)	Cameroon	Penicillins 34.1% Fluoroquinolones 3% Trimethoprim/Sulphonamides 38.8%	Community pharmacies 62% Leftovers from previous treatment 7.7% Friends/relatives 10.9% Chemist shops 19.4%
Amin et al, 2019 (93)	Cameroon	Penicillins 32.4%	Community pharmacies 55.1% Patent Medicine Stores 34.2% Health Workers 7.1% Friends 3.6%
Bunduki et al, 2017 (94)	DR Congo	Penicillins 75.1% Tetracyclines 40.8% Fluoroquinolones 54.1% Macrolide 51.5% Trimethoprim/Sulphonamides 54.1% Imidazoles 37.9%	Community pharmacies Patent medicine stores Public hospital pharmacies Private health facilities
Elden et al, 2020 (86)	Egypt	Penicillins 47.9% Macrolides 2.1%	Community pharmacies 91.7%
El-Hawy et al, 2017 (87)	Egypt	Penicillins (60.3%)	Community pharmacies 56.8% Leftovers from previous treatment 12.3%
Ateshim et al, 2019 (109)	Eritrea	Penicillins 84.1% Tetracyclines 2.5% Sulphonamides 2.1% Imidazoles 1.7	Community Pharmacies 68.0% Leftovers from previous treatment 15.2% Friends/relatives 10.4%
Bogale et al, 2019 (110)	Ethiopia	Penicillins 67.2% Fluoroquinolones 23% Sulphonamides 40%	Community pharmacies 82.3% Patent medicine stores 2% Private health facilities 11% Public hospital pharmacies 3.1%
Erku et al, 2017 (111)	Ethiopia	Penicillins 72% Tetracyclines 19% Fluoroquinolones8.9% Imidazoles 11%	Community pharmacies 36.8% Health workers (44.1%) Family/friends (19.1%)
Eticha et al, 2014 (112)	Ethiopia	Penicillins 51.7% Fluoroquinolones 12.9% Imidazoles 5.5% Tetracyclines 5.5%	Community pharmacies 83% Patent medicine store 58.9% Friends/family 29.5% Leftovers from previous treatment 28.6%
Donkor et al, 2012 (95)	Ghana	Penicillins 46.9% Amphenicols 14.9% Tetracyclines 8.5% Trimethoprim/Sulphonamides 3.1%	NR
Nyambega et al, 2017 (113)	Kenya	NR	Community pharmacies 45% Leftovers from previous treatment 22% Patent medicine stores 11% Friends/relatives 22%
Ghaieth et al, 2015 (88)	Libya	NR	Community pharmacies 74% Friends/relatives 26%
Sambakunsi et al, 2019 (115)	Malawi	NR	Community pharmacies Patent medicine stores Leftovers from previous treatment Friends/family
Olayemi et al, 2010 (96)	Nigeria	Penicillins 56.7% Tetracyclines 21.5% Fluoroquinolones 10.6% Imidazoles 25.4% Trimethoprim/Sulphonamides 20%	Community pharmacies 55.8% Public hospital pharmacies 13% Private health facilities 1.8% Patent medicine stores 32.1% Leftovers from previous treatment (14.8%)
Abdulraheem et al, 2016 (97)	Nigeria	Penicillins 54.8% Tetracyclines 13.1% Trimethoprim/Sulphonamides 13.9% Fluoroquinolones 13.1% Imidazoles 13.1%	Community pharmacies (10.9%). Patent medicine stores (20.4%) Chemist shops (58.7%) Relatives /friends (9.7%) Leftovers from previous treatment (0.8%)
Badger-Emeka et al, 2018 (98)		Penicillins (58%) Fluoroquinolones (22% Tetracycline 20% Aminoglycosides 14.75%	NR

Ehigiator et al, 2010 (99)	Nigeria	Penicillins 41% Tetracyclines 18% Imidazoles 13% Macrolides 7% Fluoroquinolones 1% Trimethoprim/Sulphonamides 19%	Community pharmacies 67.9% Chemists stores 20.8% Leftovers of previous treatment 10.4% Public hospital pharmacy 0,9%
Israel et al, 2015 (100)	Nigeria	Penicillins 38.3% Nitroimidazoles 27.6% Fluoroquinolones 14.6% Trimethoprim/Sulphonamides 14.9% Tetracyclines 3.1%	Community pharmacies 19.9% Patent medicine stores 39.3% Family/friends 19.5% Leftovers from previous treatment 19% Public hospital pharmacies 1.6% Street vendors 0.8%
Fadare et al, 2011 (101)	Nigeria	Penicillins 45.6% Nitroimidazoles 17.6% Fluoroquinolones 8.8% Trimethoprim/Sulphonamides 11.8% Tetracyclines 8.8%	Community pharmacies 16.2% Patent medicine stores 19.1% Leftovers from a previous treatment 1.5%
Sapkota et al, 2010 (102)	Nigeria	Penicillins Tetracyclines Imidazoles Fluoroquinolones	Community pharmacies Private health facilities Public hospital pharmacies Chemists shops Friends/relatives Health workers Street vendors
Umar et al, 2018 (103)	Nigeria	Penicillins Nitroimidazoles Fluoroquinolones Trimethoprim/Sulphonamides Tetracyclines Macrolides	Community pharmacies 46.8% Chemists shops 25.5% Patent medicine stores 19.2% Street hawkers 1.5% Public hospital pharmacies 7.5% Leftovers from previous treatment
Yusuf et al, 2019 (104)	Nigeria	Penicillins 54% Nitroimidazoles 6.3% Trimethoprim/Sulphonamides 10.3% Tetracyclines 28%	NR
Tuyishimire et al, 2019 (116)	Rwanda	Penicillins 60.9% Fluoroquinolone 1.5% Trimethoprim/Sulphonamides 1.5% Tetracyclines 2.9%	Community pharmacies 72.46% Friends/relatives 13.04% Leftover from previous treatment 7.3%
Bassoum et al, 2019 (107)	Senegal	NR	Community pharmacies 81% Friends/ relatives 12% Leftovers from previous treatments 5% Patent medicine stores 2%
Awad et al, 2005 (89)	Sudan	Penicillins 23.1% Fluoroquinolones 6.1% Tetracyclines 6.1% Macrolides 3.3%	Community pharmacies 68.8% Relatives and friends 19.2% Leftovers from a previous treatment 12%
Awad et al, 2007 (90)	Sudan	Penicillins 56.7% Fluoroquinolones 3% Tetracyclines 1.3% Macrolides 16%	Community pharmacies 90.0% Relatives/friends 10.0%
Ahmed et al, 2014 (91)	Sudan	Penicillins 38% Fluoroquinolones 3.4% Tetracyclines 15% Macrolides 1.7%	Community pharmacies 72% Family/friends 17% Leftovers from previous treatment 11%
Horumpende et al, 2018 (117)	Tanzania	Penicillins 46% Nitroimidazoles 10% Fluoroquinolones 1% Tetracyclines 5%	NR
Kajeguka et al, 2017 (118)	Tanzania	NR	Community pharmacies 72% Friends/relatives (18.0% Leftovers from previous treatment (9.9%)
Ocan et al, 2014 (119)	Uganda	Penicillins 28.9% Imidazoles 12.9% Fluoroquinolones 2.8% Trimethoprim/Sulphonamides 12.2% Tetracyclines 2.3% Macrolides 1.3%	Community pharmacies 68.4% Leftovers from previous treatment 17.2% Public facility pharmacies 16.9% Home medicine cabinets 16.7% Private health facilities 9.3%
Gebeyehu et al, 2015 (120)	Ethiopia	Penicillins 75.5% Imidazoles 2.3%	Community pharmacies 15.5% Friends/relatives 15.7%

		Fluoroquinolones 7.2% Tetracyclines 10.6%	
Hounsa et al, 2010 (108)	Ivory Coast	Penicillins Trimethoprim/Sulphonamides Tetracyclines	Patent medicine stores 13.7% Street vendors 11.2%
Mate et al, 2019 (123)	Mozambique	NR	Community pharmacies 74.2% Patent medicine stores 3.2% Home medicine cabinets 1.6%
Ajibola et al, 2018 (105)	Nigeria	Penicillins 48.1% Imidazoles 18% Fluoroquinolones 18.7% Trimethoprim/Sulphonamides 12% Tetracyclines 11.4%	Community pharmacies 48.4% Patent medicine stores 40% Street vendors 9.4%
Khalid et al, 2019 (106)	Nigeria	Penicillins 32.6% Fluoroquinolones 22.6% Trimethoprim/Sulphonamides 19.5% Tetracyclines 21.3%	Community pharmacies 29.4% Patent medicine stores 75.4% Family/friends 10.4% Leftovers from previous treatment 9.9% Public hospital pharmacies 7.2% Street vendors 1.4%

NR, Not Reported

Source of antibiotics used for self-medication

Thirty-two studies provided information on the main sources of antibiotics used for SMA. These include community pharmacies (CPs; 31 studies), family/friends (20 studies), leftover antibiotics from previous treatments (19 studies), patent medicine stores (PMS; 18 studies), hospital pharmacies (eight studies), street vendors (seven studies), private health facilities (six studies), chemist shops (five studies), healthcare workers (three studies) and home medicine cabinets (two studies; Figure 5).

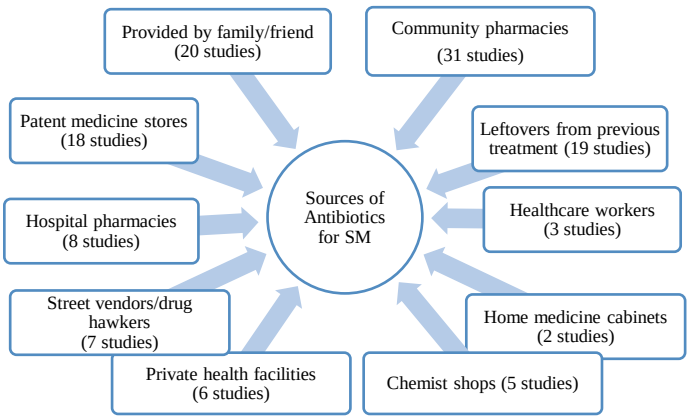

Figure 5. Sources of antibiotics used for SM in Africa

Reasons for SMA

Twenty-nine studies reported reasons why people opted to self-medicate with antibiotics. These reasons include past or prior experience with using similar symptoms or antibiotics (22 studies), additional cost incurred from facility charges (18 studies), long waiting time required to consult at health facilities (18 studies), illness perceived as mild by the patient (14 studies), advice from friend or relative (9 studies), lack of time to consult (8 studies), assumed knowledge on antibiotics use (5 studies), financial constraint (5 studies), nonchalant attitude of health workers (8 studies), lack of confidence in the healthcare system (6 studies), difficulty access to health facility due to remoteness (9 studies), easy access to antibiotics due to non-prescription sales (8 studies), emergency relief of symptoms (8 studies) and poorly staffed and equipped hospitals (3 studies) (Figure 6).

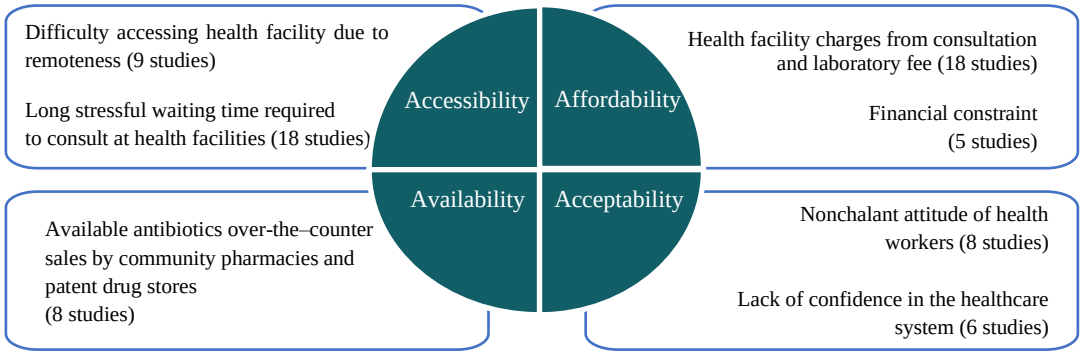

Figure 6. Reasons for SMA categorized using the modified conceptual framework of access to healthcare

Common symptoms/illnesses that resulted in SMA

The most common indications for SMA reported were upper respiratory tract symptoms/infections (common cold, cough, catarrh/runny nose, nasal congestion, sore throat, rhinitis, throat pain, tonsillitis; 27 studies), followed by gastrointestinal tract symptoms (diarrhoea, abdominal pain, vomiting; 25 studies), fever or febrile illnesses (18 studies), body aches (headache, toothache, joint pains, malaise; 15 studies), skin injuries, infections and rashes/acne (15 studies), urogenital tract symptoms (10 studies), sexually transmitted infections (five studies), eye infections (five studies), dental infections (four studies), and menstrual symptoms (three studies).

Factors associated with SMA

Twenty-one studies reported results of multivariable logistic regression analysis to determine factors associated with SMA. No education or low educational status was the most frequently reported factor in nine studies [38, 39, 45, 48-50, 53, 59, 63]. Other associated factors reported were low income or unemployment [60, 63], remoteness of health facilities [56, 61], and perceived long waiting time at health facilities [51, 61]. Some factors, such as sex and age showed contradictory results: male sex was reported in five studies [40, 48, 51, 53, 61] and female sex in two other studies [28, 59], age <30 years was reported in three studies [25, 50, 63] whilst age 30–60 years was reported in two studies [28, 59] (Table 5).

Table 5. Factors associated with SMA

Setting	Reference	Variable associated with SMA	Adjusted OR (95% CI)
Household	Awad et al, 2005 (89)	Female gender	1.50 (1.16, 1.87)
		Age range 40 -59	2.10 (1.50, 3.00)
	Ateshim et al, 2019 (109)	Male gender	1.81 (1.01, 3.26)
		Non-knowledgeable	2.13 (1.12, 4.05)
		Negative attitude	7.47 (4.54, 12.29)
	Bogale et al, 2019 (110)	Age 18 – 30	8.45 (2.55, 27.96)
		No education	6.39 (1.45, 28.19)
		Low income	2.55 (1.18, 5.50)
	Erku et al, 2017 (111)	Low educational status	5.01 (2.62, 9.34)
		Employed	2.12, (1.81, 7.29)
		Unsatisfied with healthcare services provided	5.41 (2.71, 14.21)
	Owour et al, 2015 (114)	Sexually transmitted infection	1.90 (1.00, 3.40)
		Health facility is far	2.80 (1.50, 5.01)
	Sambakunsi et al, 2019 (115)	Stocking antimicrobials at home	2.72(1.09, 6.76)
	Horumpende et al, 2018 (117)	Age range 30 – 60 years	1.73 (0.86, 3.50)
		Female gender	1.09 (0.80, 1.79)
		Unmarried	1.14 (0.80, 2.75)
		Low educational status	1.45 (0.46, 4.51)

	Kajeguka et al, 2017 (118)	Unemployed	11.10 (1.09, 11.30)
	Ocan et al, 2014 (119)	Male gender	2.03 (1.33, 3.08)
		Hospital drugs don't work	1.82 (1.09, 3.04)
		Advice from relatives/friends	2.91 (1.58, 5.34)
		Previous experience	2.49 (1.59, 3.90)
		Long-distance to the health facility	2.33 (1.58, 3.41)
		Long waiting time at the hospital	2.44 (1.54, 3.88)
	Gebeyehu et al, 2015 (120)	< 25 years	4.45 (1.54, 12.85)
		25 – 34 years	2.73 (1.03, 7.24)
		Poor educational status	4.21 (1.47, 12.07)
		Engaged with a regular job	1.94 (1.13, 3.32)
		Unsatisfied with healthcare services	3.51 (2.14, 5.78)
	Owuor et al, 2019 (122)	None	
	Mate et al, 2019 (123)	Male gender	1.88
		Low educational status	2.60
University	Elden et al, 2020 (86)	Urban resident	1.60 (1.10, 2.30)*
	Awad et al, 2007 (90)	Age range 21 – 31	1.36 (1.03, 1.81)
		Private university	1.52 (1.15, 2.02)
	Sapkota et al, 2010 (102)	lower levels of education	2.80 (1.10, 7.10)
		Non-science students	1.58 (1.03, 2.50)
	Umar et al, 2018 (103)	None	
	Eticha et al, 2014 (112)	Protestant religion	2.26 (1.19, 4.27)
Others	Abdulraheem et al, 2016 (97)	Male gender	1.56 (1.48, 1.64)
		Tertiary education	1.32 (1.18, 1.96)
		Productive cough	1.68 (1.32, 1.96)
		Sore throat	1.84 (1.63, 2.51)
		Unremitting fever	1.48 (1.22, 1.96)
	Bassoum et al, 2019 (107)	No education	2.70 (1.50, 4.80)
	Hounsa et al, 2010 (108)	Low educational level	1.42 (1.14, 1.77)
		Purchase of antibiotics at the market	1.86 (1,01, 3,42)
	Gebrekirstos et al, 2017 (121)	Male gender	1.72 (1.21, 2.44)
		Self-perceived waiting time	1.92 (1.20, 3.09)

Note: CI, Confidence Interval, OR, Odds Ratio

Discussion

This systematic review analysed the extent to which SMA is practised across Africa, the sources of SMA and the main reasons reported why people self-medicate with antibiotics. The overall median prevalence of SMA in Africa we found is higher than that reported in systematic reviews from South East Asia and the Middle East [7, 67]. A high prevalence of SMA in Africa can be linked to population growth, inequities in access to health care and weak healthcare systems, coupled with poorly regulated procurement, dispensing and use of antibiotics, and the huge role of the informal health sector [5, 68]. This high prevalence could also be related to the high burden of infectious diseases warranting a greater use of antibiotics. Comparing median prevalence estimates by sub-regions found that the highest median prevalence rates were reported from Western Africa, followed by Northern Africa and Eastern Africa. In Africa, socio-economic determinants of health vary from sub-region to sub-region, and from country to country. These are associated with the structure and conditions of health systems, and the health-seeking behaviours of people [5]. There is also variation in the way antibiotic sales are regulated across sub-regions and countries in Africa. In most African countries, antibiotics are available over-the-counter and can be obtained from CPs and PMS without prescription, similar to conditions in other LMIC in the Middle East and South East Asia regions, explaining the high prevalence rates observed [5]. Poor regulation of antibiotic sales resulting from the absence of policies or laxity in law enforcement makes antibiotics easily available for self-medication [17]. A different scenario occurs in high-income countries, where non-prescription sales of antibiotics are commonly prohibited and a low prevalence of SMA is observed [69, 70]. Activities that limit the availability of antibiotics without medical prescription could include government inspections, retention of medical prescriptions in pharmacies, involvement of pharmacists in designing interventions, and educational interventions [71]. Without government inspections, many

CPs may tend to dispense antibiotics based on financial motivation and not strictly on medical indications [17]. Pharmacists working in CPs should be sensitised to avoid non-prescription sales, especially of WHO Watch and Reserve group antibiotics.

Financial constraints, limited access to health care and easy access to antibiotics from CPs and PMS due to lack of regulatory measures were the most frequently cited reasons for SMA in Africa. We identified the nonchalant attitude of healthcare workers towards patients, not involving them in decision making as one of the main causes leading to a lack of trust in healthcare workers. Patient-centred care, though an important component of the acceptability of health services, is still grossly lacking among many health workers especially in Africa [72]. Due to the huge patient load, many medical doctors do not have enough time to properly communicate with patients or caregivers, and they often focus mainly on the biomedical aspects of health and fail to integrate psychosocial aspects of care. Coupled with all the other bottlenecks encountered in the entire health care delivery in resource-limited settings, most patients leave the consultation office unsatisfied and this reduces trust and acceptability of health services [72]. Many countries in Africa have weak and poorly developed local health systems characterised by lack of facilities and poor quality of service delivery. This negatively affects health-care seeking behaviours and causes many people to go for the option of purchasing antibiotics directly from CPs and PMS, which are easy to access and cheaper. Another major reason cited amongst top enablers of SMA is the reliance on past experiences. When people suffer from recurrent or chronic medical problems, they easily develop a habit of self-medicating, which is facilitated if they can get drugs over-the-counter. They often rely on their prior successes, hoping that the outcome will always remain the same with all disease episodes.

Low educational status, low income or unemployment and inaccessibility to health facilities or health personnel were reported as factors influencing the practice of SMA in Africa. Similar results were observed in a previous review among households in developing countries [73]. Low educational status is the most frequently reported factor associated with SMA, warranting the need to promote literacy among communities in Africa and sensitisation of the general public as a vital strategy to also reduce SMA. Illiteracy is a driver to SMA as individuals and entire communities have less opportunity to be aware of the health risks associated with SMA [5]. Special attention should be given to educating the public and healthcare providers on drugs used for self-medication. Accessibility, affordability and conditions of health facilities, and health-seeking behaviours were also among the factors identified in LMIC [17]. A multicentre study carried out in Europe revealed that higher gross domestic product and dispensing the exact quantities of prescribed doses were independently associated with a lower likelihood of SMA, whilst the perceived availability of antibiotics over-the-counter was a key enabling factor for SMA [74]. High-income countries have well-structured health systems with good healthcare infrastructures, adequate access to healthcare services and good health insurance coverage reflecting the high gross domestic product and resulting in low prevalence of SMA [69].

SMA in Africa occurs for many different indications and with different antibiotics. In this review, penicillins were the most widely used class of antibiotics for SMA in Africa, similar to what was reported in other reviews [4, 70, 75]. Penicillins are widely used for SMA because they have fewer side effects and are cheaper than other classes of antibiotics [4]. Even though WHO recommends that Watch Group antibiotics like fluoroquinolones or macrolides should be restricted to prescription-only [76] due to their potential to develop resistance, many studies reported their use for SMA in Africa. Fortunately, Reserve Group antibiotics were rarely reported for SMA,

presumably because of their rare availability, their frequent formulation as intravenous injections only, and their high cost.

CPs and PMS were the main sources of antibiotics used for self-medication. Controlling over-the-counter sales of antibiotics in Africa can be a useful strategy to mitigate SMA. This process has proven successful in High Income countries where it is done by engaging pharmacists in the development of interventions, retention of medical prescriptions in pharmacies, regular inspections of pharmacies by the government, and media campaigns in communities [71]. Limiting access to over-the-counter antibiotics without improving access to health care, in general, may not be a tangible solution in resource-limited settings like Africa where many communities are experiencing a lack of medical doctors. This problem can be addressed with task-shifting, thereby authorising pharmacists and state-registered nurses to prescribe and dispense Access Group antibiotics. Patent medicine stores are community retail stores managed often by non-qualified personnel and are prohibited in many African countries. Unqualified staff involved in sales of antibiotics do not have sufficient knowledge and skills to properly counsel patients on antibiotic use, control the dosages dispensed, and assess the quality of antibiotics sold. Using leftover antibiotics and old prescriptions is an indication of inappropriate antibiotic usage and a lack of proper education. Preventing reuse of leftovers can be another effective way of preventing SMA [74]. This can be achieved by counselling patients when dispensing antibiotics and ensuring that the quantity dispensed corresponds to that prescribed and encouraging the return of uncompleted antibiotics in CPs against financial reimbursement. Strengthening regulations on dispensing practices that enables pharmacists to dispense exact antibiotics doses as prescribed and sensitisation of patients during consultations will help reduce the leftovers antibiotics used for self-medication.

Limitations

Some of the limitations of this systematic review included uneven regional distribution of studies. Studies included in this review came from 19 of the 54 African countries with over 80% of the studies from Western and Eastern Africa and over 50% of the studies just from 4 countries (Nigeria, Ethiopia, Sudan and Kenya). The over representation of Nigeria could explain the relatively high median prevalence in Western Africa compared to other sub-regions. Even though we have formulated conclusions for the entire continent and sub-regions, we are aware that studies are not randomly distributed, and more studies were probably carried out in areas where high SMA was suspected. There are limitations introduced by the potential biases from individual studies. Fifteen studies included had a moderate risk of bias and one study had a high risk of bias. These biases resulted from variation in the selection of participants, for example, non-random sampling procedures to recruit participants, no record of recall period, potential social desirability and failure to validate survey questionnaires. Furthermore, some studies did not use the correct case definition of SMA, as they indiscriminately used either antimicrobials or antibiotics and without specifying the study duration. Many studies reported a recall period of more than 6 months, whilst some studies did not report the recall period at all.

Conclusion

The prevalence of SMA in Africa is high and varies across sub-regions with the highest prevalence reported in Western Africa. Drivers for SMA comprise of socio-economic factors elucidated by low educational status and financial constraint, limited access to health care characterised by high out-of-pockets payments, absence of patient-centred care, poor health-seeking behaviours and inadequate policies regulating the sales of antibiotics or poor implementation of existing regulations. There will be no one-size-fits-all strategy to address SMA in Africa ensuring effective and sustainable control. Tackling this problem, therefore, requires a multifaceted approach that is user-

centred and context-specific, addressing various actors and stakeholders ranging from antibiotic users to dispensers and policymakers.

Acknowledgement
We acknowledge Tine Verdonck for her contribution to the analysis and interpretation of the meta-analysis.

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Page 86: Informal medicine vendor, Nanoro, Burkina Faso, January 2023. Photo by Brecht Ingelbeen

7- Antibiotic use prior to seeking medical care in patients with persistent fever: a cross-sectional study in four low- and middle-income countries

Published 11 November 2020 in Clinical Microbiology and Infection, doi:10.1016/j.cmi.2020.11.003

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Abstract

Objectives

Community-level antibiotic use contributes to antimicrobial resistance, but is rarely monitored as part of efforts to optimize antibiotic use in low- and middle-income countries (LMICs). We investigated antibiotic use in the 4 weeks before study inclusion for persistent fever.

Methods

The NIDIAG-Fever (Neglected Infectious diseases DIAGnosis-Fever) study investigated aetiologies of infections in patients ≥5 years old with fever ≥1 week in six healthcare facilities in Cambodia, the Democratic Republic of the Congo (DRC), Nepal, and Sudan. In the present nested cross-sectional study, we describe prevalence and choice of antibiotics before and at study inclusion, applying the Access/Watch/Reserve (AWaRe) classification of the WHO List of Essential Medicines. Factors associated with prior antibiotic use were analysed.

Results

Of 1939 participants, 428 (22.1%) reported the prior use of one or more antibiotics, ranging from 6.3% (24/382, Cambodia) to 35.5% (207/583, Nepal). Of 545 reported antibiotics, the most frequent were Watch group antibiotics (351/545, 64.4%), ranging from 23.6% (DRC) to 82.1% (Nepal). Parenteral administration ranged from 5.9% to 69.6% between study sites. Antibiotic use was most frequent among young patients (5–17 years of age; risk ratio 1.42, 95%CI 1.19–1.71) and men (RR 1.29; 95%CI 1.09–1.53). No association was found with specific symptoms. Of 555 antibiotics started before study inclusion, 275 (49.5%) were discontinued at study inclusion.

Conclusions

Watch antibiotics were frequently used, and discontinued upon study inclusion. The antibiotic use frequency and choice varied importantly between LMICs. Data on local antibiotic use are essential to guide efforts to optimize antibiotic use in LMICs, should not be restricted to hospitals, and need to take local healthcare utilization into account..1016/j.cmi.2020.11.003

Introduction

Antibiotic use is associated with the development and spread of bacterial resistance to antibiotics (AMR). Monitoring antibiotic use is one of five objectives of the World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance [1]. Low- and middle-income countries (LMICs)

are hit hardest by AMR infections in terms of incidence of infections prone to AMR, and in terms of the AMR prevalence among underlying pathogens [2, 3, 4, 5]. The most critical AMR pathogens are typically community-acquired [6, 7, 8], and up to 80% of healthcare is sought outside official healthcare facilities at private pharmacies or clinics, or informal drug sellers [9, 10, 11]. Although such antibiotic use without established diagnosis increases the risk of acquiring an AMR infection, current efforts to rationalize antibiotic use in LMICs focus exclusively on secondary or tertiary care hospitals [12]. In many high-income and some middle-income countries, nationwide human antibiotic use has been estimated from wholesaler sales data, thus considering the 'official' medicine supply chain [13],[14]. In LMICs, official antibiotic use is currently not systematically monitored, let alone use of antibiotics from private or informal healthcare providers at community level.

To facilitate monitoring of antibiotic use, since 2017 the WHO categorized the antibiotics on the Essential Medicines List into three groups using the Access/Watch/Reserve (AWaRe) classification: 'Access' corresponds to antibiotics for empirical treatment of the most common or severe clinical syndromes, widely accessible at all healthcare levels; 'Watch' includes the highest priority antibiotics, most at risk of becoming ineffective due to increasing AMR, to be actively monitored; and 'Reserve' are last-resort antibiotics restricted to specific healthcare levels [15],[16].

The Neglected Infectious Diseases DIAGnosis-Fever (NIDIAG-Fever) study investigated the aetiologies of infections in patients with persistent fever admitted to hospitals in four LMICs (ClinicalTrials.gov NCT01766830; http://www.nidiag.eu). We estimated and compared patients' antibiotic use prior to study inclusion, identified factors associated with community- or primary-care-level use of antibiotics, and analysed how that related to empirical antibiotic treatment in hospitals.

Methods

Patient population

All participants to the NIDIAG-Fever study were included for this nested cross-sectional study of antibiotic use. Inclusion criteria were: fever ≥1 week, age ≥5 years (≥18 years in Cambodia), no existing laboratory confirmed diagnosis at the time of consultation/admission to the hospital. Patients in need of immediate intensive care were excluded. Both hospitalized and ambulatory patients could be included in the study and were evaluated for a pre-established set of priority infections [17].

Study setting

Patients were recruited in six study sites in four countries (Table 1) between January 2013 and October 2014 (For NIDIAG-Fever data collection procedures, see Supplementary Material Text S1.).

Table 1. Study site and country characteristics

Country	Cambodia	DRC	Nepal	Sudan
Study site	Sihanouk Hospital Center of HOPE, Phnom Penh	1) Hôpital Général de Mosango, Kwilu Province 2) Centre de Santé de Kasay, Kwilu Province	1)Dhankuta District hospital, Dhankuta District 2)BP Koirala Institute of Health Sciences (BPKIHS), Dharan, Sunsari District	Tabarak Allah Hospital, Gedaref Province
Type of health facility	Urban, NGO-supported referral hospital for HIV and TB care for adults	1) rural district hospital 2) rural health centre	1) rural district hospital 2) urban referral hospital	rural NGO-supported district hospital
GDP per capita, 2014	972.7 USD	397.3 USD	711.3 USD	1825.5 USD
Human Development Index, 2014	0.558	0.425	0.555	0.488

Life expectancy, 2014	68.0	60.1	70.0	67.6
Median age of the population, 2015	23.9	16.8	23.2	18.9

DRC, the Democratic Republic of the Congo; GDP per capita in constant 2010 USD; Sources: World Bank national accounts data, OECD National Accounts data files, Gapminder foundation. http://gapm.io/ilex

Data analysis

We considered as antibiotic use prior to study inclusion any antibacterial for systemic use (Anatomical Therapeutic Chemical (ATC) classification subgroup J01) started between 28 days and 1 day before enrolment. We also included reported antibiotics with a missing starting date. Any antibacterial used on day 0 or day 1 after study inclusion was considered antibiotic use at study inclusion. We excluded antibiotics for systemic use that could also be used for the treatment of tuberculosis (TB) (e.g. streptomycin) in patients with active TB. For metronidazole, we considered only oral and parenteral administration as antibiotic use, according to the WHO Essential Medicines List [16]. Antibiotic names that could not be recalled were completed by asking relatives, showing pictures of packages of circulating antibiotics, or through home visits to retrieve the medicine packages or prescriptions (DRC and Nepal), or they were recorded as 'not specified' antibiotics (Sudan). In the DRC and Sudan, antibiotics for which the name or brand could not be recalled were still recorded, but as 'not specified'. This was not done in Cambodia and Nepal, where medicines of which the name or brand could not be recalled were not recorded.

We described the frequency and choice of antibiotic use prior to study inclusion by antibiotic class, by AWaRe group, and by route of administration, comparing between countries and age groups. We used a rank-sum test to compare the time (days) from initiating antibiotic use to study inclusion. We calculated three metrics to monitor antibiotic use, proposed by Hsia et al.: the percentage of amoxicillin, the percentage of Access antibiotics, and the ratio of Access to Watch antibiotics used (access-to-watch index) [18]. The association between characteristics, clinical symptoms and signs and (Watch group) antibiotic use prior to study inclusion was analysed in univariable and multivariable analysis, using negative binomial regression. We adjusted for two potential confounders: age group (5–17 years, 18–64 years, ≥65 years) and country. Finally, we compared the distribution of antibiotics by AWaRe group prior to and at study inclusion.

Ethical considerations

The NIDIAG-Fever study protocol was approved by the ITM Institutional Review Board, the University of Antwerp Ethical Committee (EC), Belgium, the National EC for Health Research, Cambodia, the Nepal Health Research Council, the EC of the University of Khartoum, Sudan, the National Research Ethics Review Committee, Sudan, and the University of Kinshasa School of Public Health EC, DRC. Study participants provided written informed consent, stating that the clinical data could be used for studies beyond the primary NIDIAG study objectives.

Results

Participant characteristics

Of 1939 study participants, 382 (19.7%) were from Cambodia, 300 (15.5%) from the DRC, 583 (30.1%) from Nepal and 674 (34.8%) from Sudan. Children or adolescents (aged 5–17 years) were included in the DRC (137, 45.7%), Nepal (107, 18.4%) and Sudan (135, 20.0%) (Table 2). Along with age, the frequency of chronic conditions differed between the study sites. Underlying non-communicable diseases (NCDs) (17.3%) and HIV co-infection (7.1%) were frequently reported at the Cambodian site. Active TB was reported by patients in Cambodia (1.8%) and at BP Koirala Institute of Health Sciences in Nepal (BPKIHS, 0.7%).

Antibiotic use prior to consultation or admission for persistent fever

Overall, 428 patients (22.1%) reported the use of one or more antibiotics prior to study inclusion: 24 (6.3%) in Cambodia, 29 (9.7%) in the DRC, 207 (35.5%) in Nepal, and 168 (24.9%) in Sudan; 151 (35.3%) of these patients used more than one antibiotic prior to study inclusion. Use of multiple antibiotics was especially frequent in Nepal (96 patients, 46.8%) and Cambodia (ten, 41.7%), followed by the DRC (nine, 31.0%) and Sudan (36, 21.4%).

Table 2. Reported characteristics of NIDIAG-fever study participants, by study site.

Country		**Cambodia**		**DRC**				**Nepal**				**Sudan**	
Site		**Sihanouk Hospital (N=382)**		**Mosango Hospital (N=213)**		**Kasay Health Centre (N=87)**		**BPKIHS (N=430)**		**Dhankuta Hospital (N=153)**		**Tabarak Allah Hospital (N=674)**	
		n	%	n	%	n	%	n	%	n	%	n	%
Age group	5-17 years	0*	0.0	85	39.9	52	59.8	87	20.2	20	13.1	135	20.0
	18-64 yrs.	319	83.5	124	58.2	33	37.9	307	71.4	113	73.9	493	73.1
	65+ yrs.	63	16.5	4	1.9	2	2.3	36	8.4	20	13.1	46	6.8
Sex	Female	195	51.0	115	54.0	49	56.3	176	40.9	78	51.0	386	57.3
	Male	187	49.0	98	46.0	38	43.7	254	59.1	75	49.0	288	42.7
Co-morbidity	NCD	66	17.3	14	6.6	6	6.9	27	6.3	0	0.0	33	4.9
	HIV+	27	7.1	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0
	Tuberculosis**	7	1.8	0	0.0	0	0.0	3	0.7	0	0.0	0	0.0
Clinical symptom or sign	Anorexia/cachexia	306	80.1	81	38	41	47.1	224	52.1	31	20.3	464	68.8
	Respiratory	243	63.6	53	24.9	19	21.8	131	30.5	58	37.9	315	46.7
	Digestive (other)	141	36.9	63	29.6	28	32.2	97	22.6	9	5.9	332	49.3
	Headache	150	39.3	53	24.9	27	31	102	23.7	28	18.3	268	39.8
	Urinary	40	10.5	3	1.4	2	2.3	30	7	2	1.3	185	27.4
	Skin problem (incl.rash)	66	17.3	12	5.6	4	4.6	36	8.4	0	0	113	16.8
	Tonsillitis/pharyngitis	29	7.6	10	4.7	4	4.6	29	6.7	21	13.7	128	19
	Diarrhoea	33	8.6	9	4.2	4	4.6	17	4	0	0	73	10.8
	Jaundice	23	6	8	3.8	2	2.3	10	2.3	0	0	4	0.6

Co-morbidities were self-reported medical history; NCD, non-communicable disease; DRC, the Democratic Republic of the Congo; * Children 5-17 years old were not included in the study in Cambodia; ** Active tuberculosis

Of patients reporting antibiotic use prior to study inclusion at the study site, 362 (84.6%) patients were able to specify which antibiotic they used. Specifics on antibiotic names were obtained from all patients reporting antibiotic use in Cambodia and Nepal, from 27 patients (93.1%) in the DRC and 104 (61.9%) in Sudan. Of 545 reported antibiotics, cephems (185, 33.9%), fluoroquinolones (92, 16.9%), macrolides (77, 14.1%), and β-lactamase-labile penicillins (70, 12.8%) were most frequently used. Use of cephems was highest in Nepal (154, 44.5%) and consistent among patients from both study sites (45.2% at BPKIHS and 33.3% at Dhankuta Hospital). In other countries, cephem use was lower: 10.5% in the DRC, 14.8% in Sudan, and 23.1% in Cambodia. Use of fluoroquinolones ranged between 7.9% of antibiotics used in the DRC and 20.5% in Cambodia. Use of macrolides ranged between 4.1% in Sudan and 18.8% in Nepal. While β-lactamase-labile penicillins were the most frequently used antibiotic class in Sudan (40.2%), they were rarely used in Cambodia (2.6%) and Nepal (4.0%). However, amoxicillin was used in combination with a β-lactamase inhibitor (β-lactam combination) in 17.9% of patients in Cambodia and 4.6% in Nepal. Metronidazole (nitroheterocyclics class; active on anaerobic bacteria and protozoa) was the most frequently used antibiotic in the DRC (34.2%) but was hardly used in Nepal (1.7%) or Cambodia (2.6%). Carbapenems (imipenem) were used by one patient in Nepal (0.3%). Glycopeptides (vancomycin) were used by three patients, all in Nepal (0.9%).

Oral (335, 60.4%) and parenteral administration (220, 39.6%) was reported. The proportion of parenteral administration varied widely between sites, and also within countries; in the DRC it ranged from 5.9% to 69.6%, in Nepal from 9.5% to 51.6%, in Sudan it was 27.6% and in Cambodia 35.9% (Fig. 1).

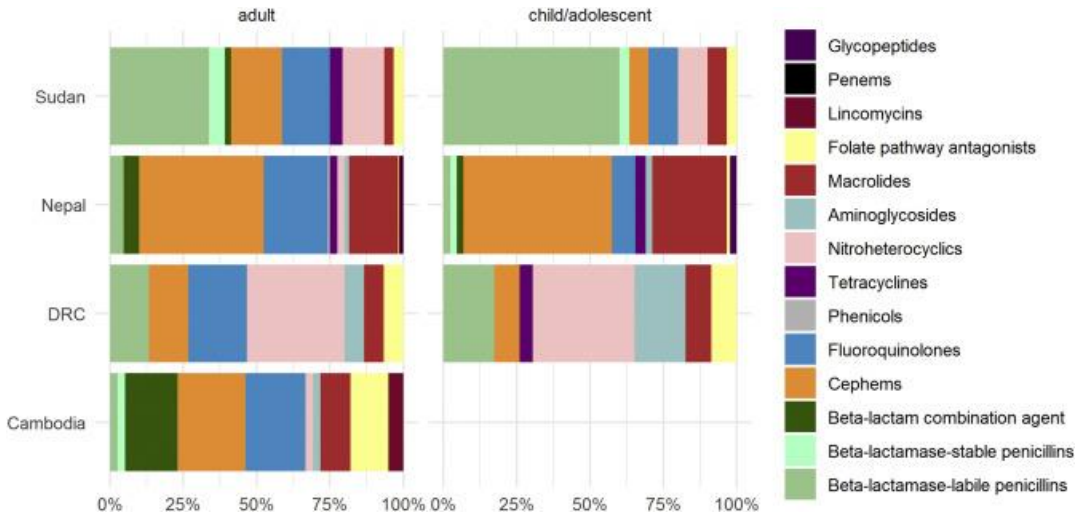

Figure 1. Distribution of antibiotic classes used 28 days prior to study inclusion, by country and by age group (5–17 years, ≥18 years). Non-specified antibiotics (n = 87) are excluded.

Distribution of AWaRe antibiotics

When classifying the antibiotics by AWaRe group, 188 (34.5%) were Access antibiotics. Most frequently reported were Watch antibiotics (351, 64.4%). Use of Watch antibiotics was highest in Nepal (284, 82.1%), with ceftriaxone (97), cefixime (45) and ofloxacin (38) as main contributors, followed by Cambodia (20, 51.2%), Sudan (38, 31.1%) and DRC (9, 23.6%). Ceftriaxone (cephem), azithromycin (macrolide), ciprofloxacin, ofloxacin (fluoroquinolones) and cefixime (cephem) were all used more frequently than any Access antibiotic. One (0.2%) Reserve antibiotic was used: cefepime (fourth-generation cephem) in Cambodia. Five (0.9%) did not belong to the WHO essential medicines list and were therefore not classified (two oral cefuroxime, one parenteral lincomycin, one oral lincomycin, and one oral tetracycline) (Fig. 2).

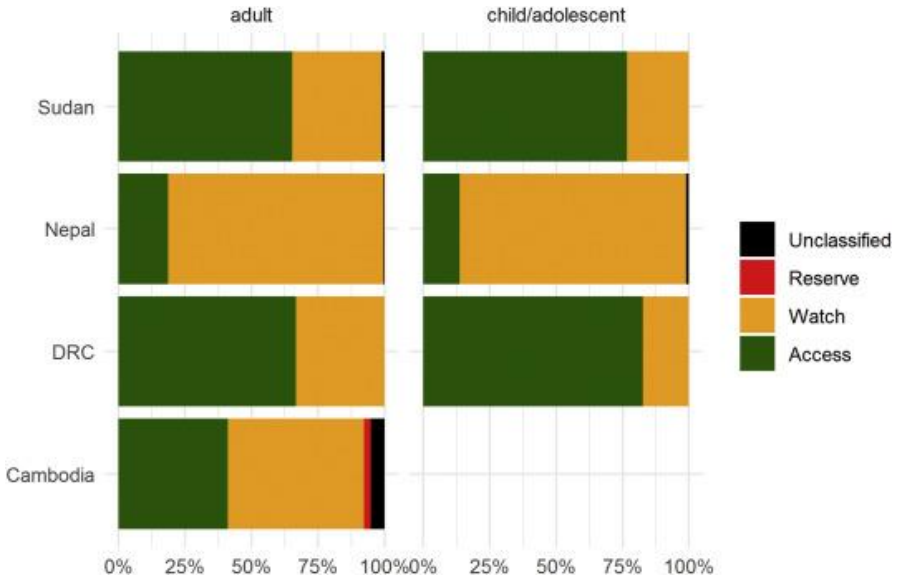

Figure 2. AWaRe (Access, Watch, Reserve) group distribution of antibiotics used 28 days prior to study inclusion, by country and by age group (5–17 years, ≥18 years). Non-specified antibiotics (n = 87) are excluded.

Among adults, amoxicillin percentages were 2.6% (Cambodia), 13.3% (DRC), 3.9% (Nepal) and 10.9% (Sudan), Access percentages were 41.0% (Cambodia), 66.7% (DRC), 18.5% (Nepal) and 65.2% (Sudan), and access-to-watch indices were 0.8 (Cambodia), 2.0 (DRC), 0.2 (Nepal) and 1.9 (Sudan). Among adolescents, amoxicillin percentages were 8.6% (DRC), 2.2% (Nepal) and 2.7% (Sudan), Access percentages were 82.6% (DRC), 13.8% (Nepal) and 76.7% (Sudan), and access-to-watch indices were 4.8 (DRC), 0.2 (Nepal) and 3.3 (Sudan).

Time between initiating antibiotic use and consultation/admission with persistent fever

Patients started antibiotics a median 6 days prior to study inclusion (interquartile range (IQR) 3–11; range 1–28). This median time span between starting an antibiotic and study inclusion was 7 days (IQR 3–13) among adults and shorter, 5 days (IQR 2–8), among children and adolescents ($p < 0.01$). In Cambodia this median time span was 7 days (IQR 3–13), in the DRC 3 days (IQR 1–7), in Nepal 4 days (IQR 2–7), and in Sudan 9 days (IQR 6–16) (Fig. 3a). Access antibiotics were started a median 6 days (IQR 3–11) prior to study inclusion; Watch antibiotics 3 days (IQR 1–7) (Fig. 3b).

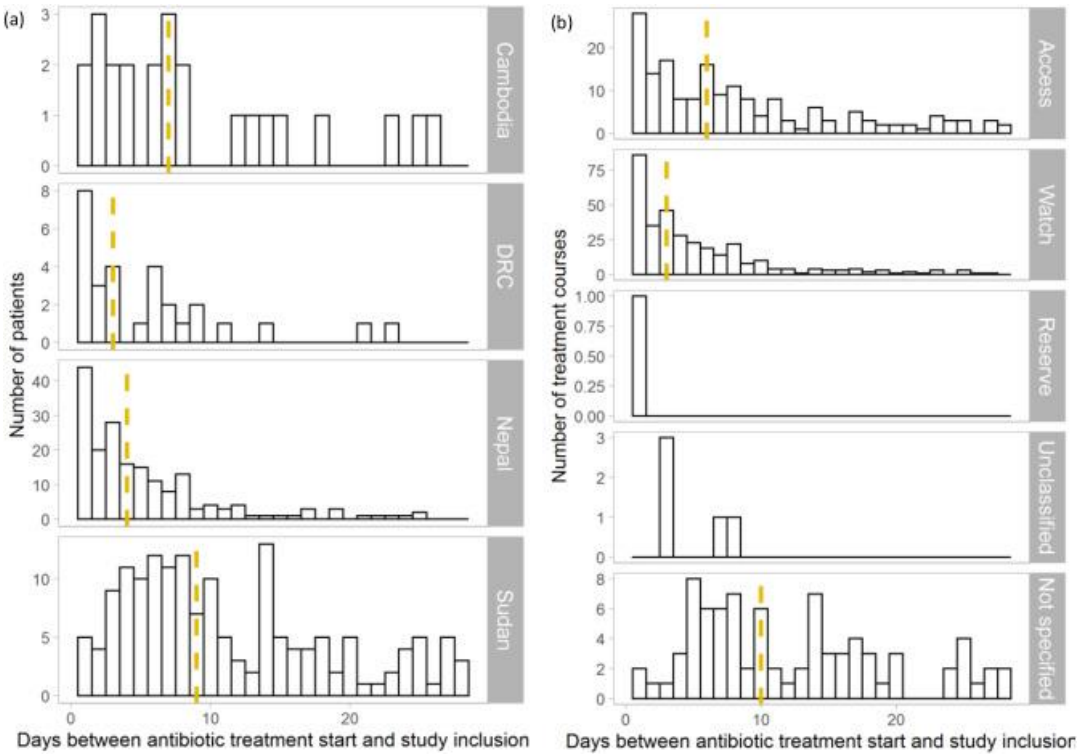

Figure 3. Histogram of the time (in days) between the start of antibiotic treatment and study inclusion of patients, by country (a), and of treatment courses, by AWaRe group (b). Dashed yellow lines are medians.

Factors associated with prior antibiotic use

Antibiotic use prior to study inclusion was more frequent in children and adolescents than in adults (adjusted risk ratio (aRR) 1.44, 95%CI 1.15–1.77), but threefold less in those over 65 years of age (aRR 0.37, 95%CI 0.20–0.61). Men reported prior antibiotic use more frequently than women (aRR 1.25, 95%CI 1.03–1.52). We found no clinical signs or symptoms to be strongly associated with antibiotic use prior to study inclusion. Patients with tonsillitis or pharyngitis reported prior antibiotic use most frequently (27.1%), but the association was not significant when controlling for age groups and study country (Table 3).

Table 3. Characteristics, clinical symptoms and signs associated with antibiotic use 28 days prior to study inclusion. The clinical symptoms and signs were those reported at study inclusion, in addition to fever.

		Prior ABU (n)	No prior ABU(n)	Prior ABU (%)	Crude RR	95%CI lower	95%CI upper	Adjusted RR*	95%CI lower	95%CI upper
Age group	5-17 years	116	263	30.6	1.42	1.19	1.71	1.44	1.15	1.79
	18-64 years	299	1090	21.5	1	ref	ref	1	ref	ref
	65 or more years	13	158	7.6	0.35	0.21	0.6	0.37	0.20	0.61
Sex	Female	193	806	19.3	1	ref	ref	1	ref	ref
	Male	235	705	25.0	1.29	1.09	1.53	1.25	1.03	1.52
Underlying NCD		28	126	18.2	0.81	0.57	1.15	1.23	0.82	1.79
Clinical symptoms and signs	Anorexia/cachexia	270	877	23.5	1.15	0.97	1.37	1.34	1.09	1.65
	Skin problem	47	184	20.3	0.90	0.69	1.18	0.99	0.72	1.34
	Jaundice	9	38	19.1	0.86	0.47	1.55	1.28	0.61	2.34
	Tonsillitis/pharyngitis	60	161	27.1	1.25	0.99	1.58	1.14	0.86	1.50
	Respiratory	166	653	20.3	0.85	0.72	1.01	0.95	0.78	1.16
	Diarrhoea	35	101	25.7	1.17	0.87	1.57	1.29	0.89	1.80
	Digestive (other)	159	511	23.7	1.10	0.93	1.31	1.24	1.01	1.53
	Urinary	67	195	25.6	1.17	0.94	1.47	1.13	0.85	1.48
	Headache	125	503	19.9	0.85	0.70	1.02	0.92	0.74	1.14
	Other	358	1212	22.8	1.14	0.90	1.45	1.47	1.12	1.94

*Adjusted for age group and study country; ABU, antibiotic use; RR, risk ratio; 95%CI, 95% confidence interval; NCD, non-communicable disease

Among patients having used antibiotics prior to study inclusion, the use of Watch antibiotics was lower among children (48.3%) than among adults (61.2%, RR 0.79, 95%CI 0.64–0.97), and slightly higher among male (63.0%) than among female patients (51.3%, RR 1.23, 95%CI 1.04–1.45). We found no clinical sign or symptom to be associated with the use of Watch antibiotics (see Supplementary Material Table S3).

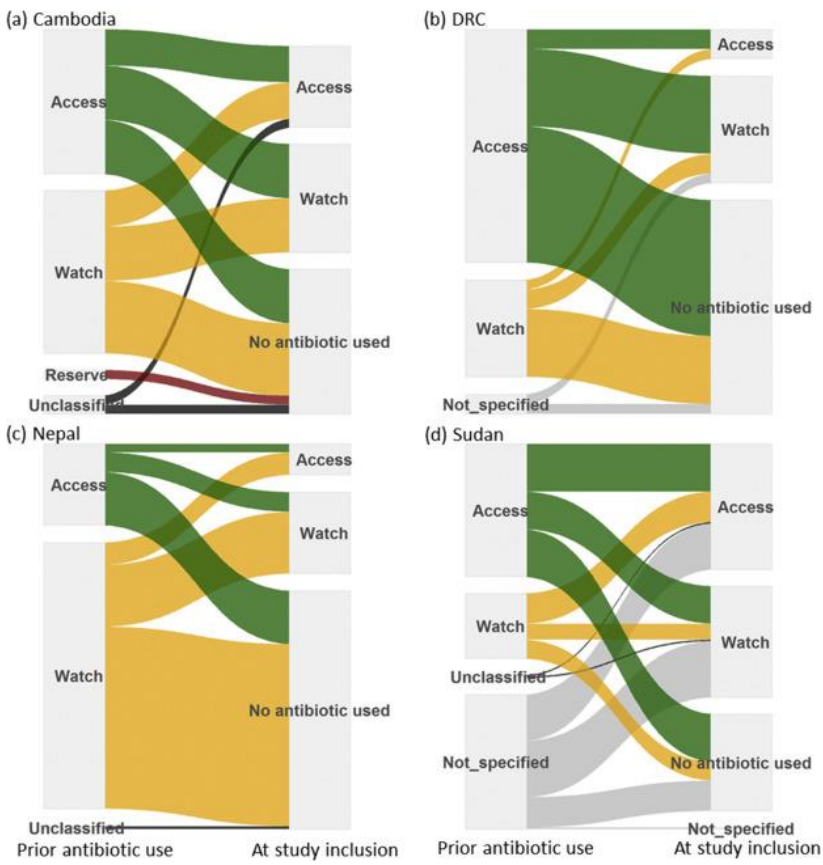

Figure 4. Sankey diagram of the distribution of antibiotics by AWaRe (Access, Watch, Reserve) group, used 28 days prior to and at study inclusion. (a) Cambodia, (b) DRC, (c) Nepal, (d) Sudan.

Changes in antibiotic use at study inclusion

Of 555 antibiotic courses used prior to study inclusion, 275 (49.5%) were discontinued and not replaced with an antibiotic at study inclusion, ranging from 29.3% (Sudan) to 68.0% (Nepal). Watch antibiotics were more frequently (60.1%) discontinued and not replaced than Access antibiotics (47.9%). Moreover, 16.0% of prior Watch antibiotics were replaced by Access antibiotics at study inclusion (see Supplementary Material Fig. S4). If an antibiotic was used at study inclusion, 121 (43.2%) were Access and 158 (56.4%) were Watch antibiotics. No Reserve antibiotics were initiated or continued at study inclusion (Fig. 4).

Discussion

We found that two thirds of antibiotics used by patients with persistent fever at community or primary healthcare level in four LMICs were Watch antibiotics—most threatened to become ineffective due to AMR—ranging from 23.6% in the DRC to 82.1% in Nepal; 40% of the antibiotics were administered intravenously. The use of first-choice antibiotics for primary care, such as amoxicillin, was below 15% in all study countries and across age groups. That we observed no differences between clinical presentations could indicate that such antibiotic use is based on availability rather than on the presenting syndrome. One in two antibiotic courses started prior to study inclusion, and even 60.1% of Watch antibiotics were discontinued following a consultation by a qualified healthcare worker, despite study clinicians frequently having to rely on just presumptive diagnoses in the absence or limited performance of diagnostic tests. The prevalence of antibiotic use prior to study inclusion, including self-medication through informal healthcare which is frequent in LMICs [14,18,19], and the proportion of Watch/Reserve group antibiotics were highest in Nepal and Cambodia.

Most studies reporting prior antibiotic use in LMICs are limited to patients with bloodstream infections, and generally they found that reported antibiotic use was higher than that in our study [20,21,22,23]. Patients with (potentially septic) shock, likely to report prior antibiotic use, were not included in the present study. Moreover, most bloodstream infections are reported in children, who also report more frequent prior antibiotic use [23,24]. Furthermore, our study found more frequent prior antibiotic use in children than in adults. In adults, the use of Watch antibiotics was surprisingly frequent, and even accounted for more than half of antibiotic treatment courses in adults in Cambodia (51.3%) and Nepal (81.1%), explained especially by the frequent use of ceftriaxone (cephem), which also resulted in frequent parenteral administration. Another study in Nepal reported that 38% of patients in private pharmacies in Nepal received antibiotics, of which over half were cephems [25]. In many settings in South-East Asia and Sub-Saharan Africa—where multidrug-resistant Gram-negative bloodstream infections are frequent but clinical microbiology capacity is absent—cephems and macrolides can be the only effective and accessible treatment options left, proving the need to carefully monitor their use [21,22].

To our knowledge, the AWaRe metrics have not previously been used for low-income or African countries, and for adult antibiotic use data, and were calculated using national level sales data. The amoxicillin and Access percentages we calculated were far lower than those observed in a paediatric antibiotic consumption study in 70 high- and middle-income countries (median 30.7% and 76.3%) [18], which also found the lowest Access-to-Watch index in Asian countries.

The antibiotic use prevalence and distribution between antibiotic groups that we have reported need to be interpreted with caution and should not be used as a standalone estimate of antibiotic use in these countries, for the following reasons. Only patients with persistent fever (eventually) seeking formal healthcare were included. Self-reporting of antibiotic use may result in an underestimation of the prevalence of actual prior antibiotic exposure [24]. The extent to which antibiotics were

recorded and verified also varied slightly among study sites, potentially resulting in an underestimation (Cambodia, Nepal) or overestimation (Sudan, DRC) of the frequency of antibiotic use. Additionally, including antibiotics for which the start date was missing might result in an overestimation of antibiotic use within the month prior to consultation, although this is likely limited since very few patients with accurate start dates reported antibiotic use from more than a month. Another limitation is that the recorded clinical signs may have been different at the time when a patient started a course of antibiotics, therefore underestimating the association between signs or symptoms and antibiotic use. Finally, study sites and populations were also different in terms of pathways of care, referral behaviour, age, co-morbidities, exposure, AMR of underlying infections [3,6,22], healthcare workers' training, role of the pharmaceutical industry on prescribing behaviour [26], and availability of diagnostics, limiting both their comparability and the external validity of our findings.

The differences in antibiotic use can indeed be partially explained by differences in fever patients' demographics, in the aetiology of febrile illness, and in the (referral) role of the study healthcare facilities, but the following determinants are likely to play a significant role: patients' and providers' illness perceptions, healthcare-seeking behaviour, self-medication, and availability and affordability of (Watch group) antibiotics at community level. Differences in accessing antibiotics at community level are also reflected in the large difference in the time between initiating antibiotic use and study inclusion at the hospital reported here, varying between a median of 3 days in the DRC and 9 days in Sudan. Across study sites, several critically important Watch antibiotics were widely used in the community, even though antibiotic use is frequently deemed non-essential or ineffective (and therefore discontinued) when qualified healthcare workers consult these patients. These findings emphasize the need to monitor and optimize community- or primary-healthcare-level antibiotic use in LMICs. The present study can serve as an excellent ‘baseline’ for monitoring community- and primary-care antibiotic use, as recommended in the 2015 WHO Global action plan on AMR.

Author contributions

BI and KK contributed equally to this study. BI wrote the original draft and edited further revisions of the manuscript and conceptualized the data analyses. KK conceptualized the methodology, collected, curated and validated the data, and revised the manuscript. KV conceptualized the research idea and methodology, curated and validated the data, undertook data analyses, revised the manuscript, and supervised the research work. BB curated and validated the data, and revised the manuscript. DM and PT collected, curated and validated the data, and revised the manuscript. SS collected and curated the data, and revised the manuscript. LVD revised the manuscript. EB and MB developed the NIDIAG study and revised the manuscript. MvdS revised the manuscript and analyses. FC was principal investigator of the NIDIAG study, developed the study, and revised the manuscript. JJ conceptualized the research idea and methodology, validated the data, revised the manuscript, and supervised the research work.

Transparency declaration

All authors declare no competing interests. This work is part of the NIDIAG European research network (Collaborative Project), supported by the European Union's Seventh Framework Programme for research, technological development, and demonstration under grant agreement no. 260260 . This work was supported by the Bacterial Infections in the Tropics research cluster , funded by the InBev-Baillet-Latour fund, Belgium . The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary data

Supplementary Text S1. Data collection

In Sudan, recruitment of patients was interrupted between April and September 2013, as a result of clinical management and laboratory testing adjustments, combined with a rainy season that rendered the study site almost inaccessible by road. No study specific treatment guidelines were implemented.

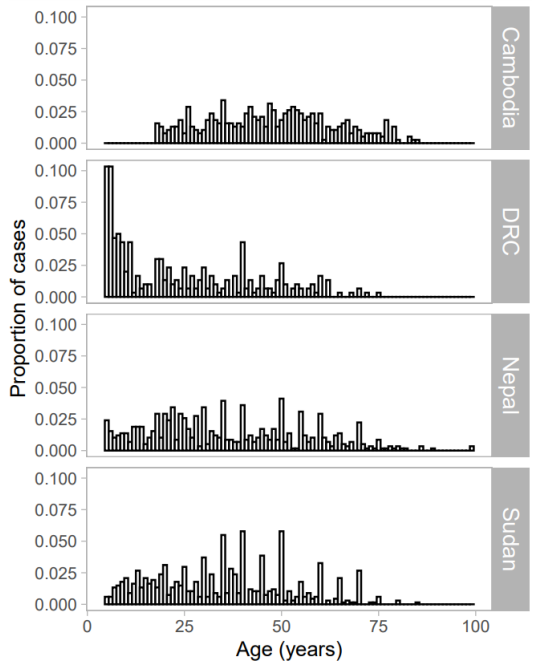
Each centre used its own or national (condition-specific) treatment guidelines whenever available.

During admission or consultation at the hospital or health centre, patients were interviewed by study physicians, using a paper-based case report form, recording age, medical history, medication use including antibiotics prior to enrolment, clinical symptoms and signs. Of antibiotics used prior to and at study inclusion, generic name, dosage, frequency, route, start and end date were recorded.

A trained pharmacist recoded reported brand names to their generic name and added antibiotic classes/groups, using the 2019 Clinical and Laboratory Standards Institute and 2019 WHO Model List of Essential Medicines AWaRe classifications.

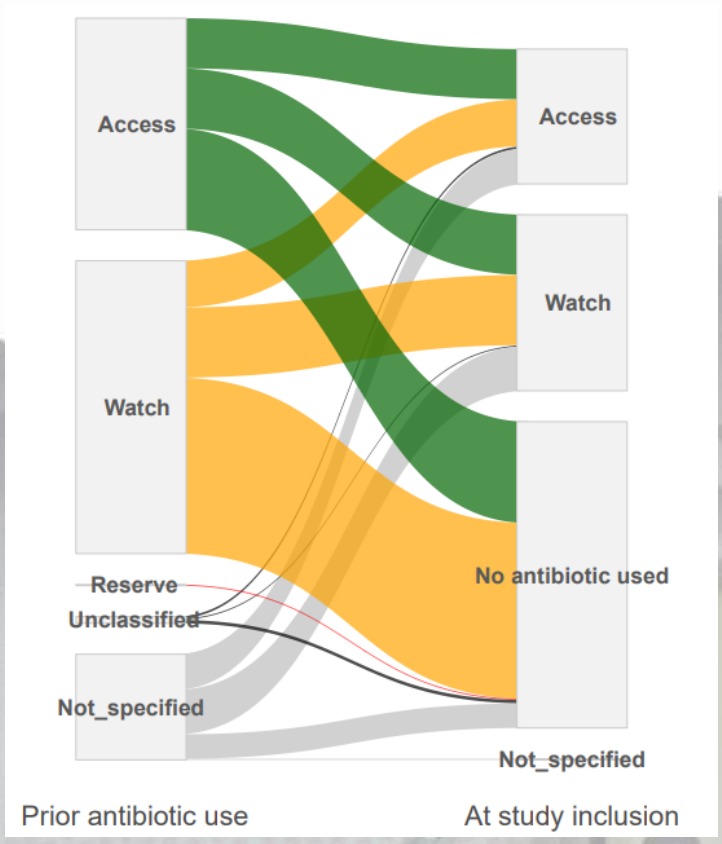
From the patients' reported medical history, we created a new composite variable underlying NCDs by combining any reported asthma, chronic obstructive pulmonary disease, cancer, epilepsy, diabetes, hypertension and other cardiovascular conditions. We also retrieved HIV disclosure and active TB infections (reported or based on ongoing TB treatment).

Supplementary Figure S2. Age distribution of NIDIAG-fever study participants by country



Supplementary Table S3. Characteristics, clinical symptoms and signs associated with the use of Watch antibiotics, among patients having used antibiotics prior to consultation. The clinical symptoms and signs were those reported at study inclusion, in addition to fever.

		Watch AB used (n)	Only Access AB used (n)	Watch AB used (%)	Crude risk ratio	95%CI lower	95%CI upper
Age group	5-17 yr	56	60	48.3	0.79	0.64	0.97
	18-64 yr	183	116	61.2	1	ref	ref
	65+ yr	8	5	61.5	1.01	0.65	1.56
Sex	Female	99	94	51.3	1	ref	ref
	Male	148	87	63.0	1.23	1.04	1.45
Clinical symptoms and signs	Anorexia/cachexia	270	877	23.5	1.15	0.97	1.37
	Skin problem (incl.rash)	47	184	20.3	0.9	0.69	1.18
	Jaundice	9	38	19.1	0.86	0.47	1.55
	Tonsillitis or pharyngitis	60	161	27.1	1.25	0.99	1.58
	Respiratory	166	653	20.3	0.85	0.72	1.01
	Diarrhoea	35	101	25.7	1.17	0.87	1.57
	Digestive (other)	159	511	23.7	1.1	0.93	1.31
	Urinary	67	195	25.6	1.17	0.94	1.47
	Headache	125	503	19.9	0.85	0.7	1.02
	Other	358	1212	22.8	1.14	0.9	1.45



Supplementary Figure S4. Sankey diagram of the distribution of antibiotics by AWaRe group used prior to and at study inclusion at the study healthcare facility

Patient exit interviews in Kavuaya health area, Kisantu health zone, DR Congo, November 2019. Photo by Brecht Ingelbeen

8- Antibiotic use from formal and informal healthcare providers in the Democratic Republic of Congo: a population-based study in two health zones

Published 20 May 2022 in Clinical Microbiology and Infection, doi:10.1016/j.cmi.2022.04.002

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Abstract

Objectives

In the Democratic Republic of Congo and other low-resource countries, community-acquired pathogens are increasingly resistant to most locally available antibiotics. To guide efforts to optimize antibiotic use to limit antibiotic resistance, we quantified healthcare provider-specific and community-wide antibiotic use.

Methods

From household surveys, we estimated monthly healthcare visit rates by provider. From healthcare visit exit surveys, we estimated prevalence, Defined Daily Doses (DDD), and Access/Watch/Reserve distribution of antibiotic use by provider. Combining both, we estimated community-wide antibiotic use rates.

Results

Of 88.7 (95%CI 81.9-95.4, 1588/31221 person-months) healthcare visits per 1000 person-months, visits to private clinics (31.0, 95%CI 30.0-32.0, 418/31221) and primary health centres (25.5, 95%CI 24.6-26.4, 641/31221) were most frequent. Antibiotics were used during 64.3% (95%CI 55.2-73.5%, 162/224) of visits to private clinics, 51.1% (95%CI 45.1-57.2%, 245/469) to health centres, and 48.8% (95%CI 44.4-53.2%, 344/454) to medicine stores. Antibiotic DDD per 1000 inhabitants per day varied between 1.75 (95%CI 1.02-2.39) in rural Kimpese and 10.2 (95%CI 6.00-15.4) in (peri-)urban Kisantu, mostly explained by differences in healthcare utilisation (respectively 27.8 versus 105 visits per 1000 person-months), in particular of private clinics (1.23 versus 38.6 visits) where antibiotic use is more frequent. The fraction of Watch antibiotics was 30.3% (95%CI 24.6-35.9%) in private clinics, 25.6% (95%CI 20.2-31.1%) in medicine stores, and 25.1% (95%CI 19.0-31.2%) in health centres. Treatment durations <3 days were more frequent at private clinics (5.3%, 9/169) and medicine stores (4.1%, 14/338) than at primary health centres (1.8%, 5/277).

Conclusions

Private healthcare providers, ubiquitous in peri-urban settings, contributed most to community-wide antibiotic use and more frequently dispensed Watch antibiotics and shortened antibiotic courses. Efforts to optimize antibiotic use should include private providers at community-level.

Introduction

In low-and middle-income countries (LMIC), with a high and persistent burden of infectious diseases, available estimates indicate >80% of bacterial bloodstream infections are resistant against common Access antibiotics, and an increasing proportion is resistant against Watch antibiotics[1–3], threatening effective treatment against bacterial infections and resulting in most deaths attributable to antibiotic resistance[4]. In the Democratic Republic of Congo (DRC), the most frequently isolated pathogens in bloodstream infections, non-typhoidal and Typhi Salmonella (respectively 66 and 10% of isolates), are increasingly resistant to fluoroquinolones (7.3% and 24.5% respectively), third generation cephalosporins (15.7% and 0.2%), and macrolides (14.9% and 0.4%), on top of widespread multidrug resistance against first-line antibiotics[5,6].

To limit increasing antibiotic resistance, a key objective of the Global Action Plan on Antimicrobial Resistance is to optimize antibiotic use[7]. In low-income countries a significant part of antibiotic use happens outside official health care facilities, through informal health seeking or self-medication[8–10], which is overlooked in rare interventions to optimize antibiotic use. Here, sales data or hospital point prevalence surveys do not allow estimating country- and community-wide antibiotic consumption[11–14]. To inform the development and targeted implementation of interventions to optimize antibiotic use in low-resource settings, we estimated antibiotic use from both formal and informal healthcare providers in DRC.

Methods

Population

The study was conducted in the Kisantu and Kimpese health zones in Kongo-Central province, 120 and 210 km Southwest of Kinshasa. In each health zone, we selected two health areas, corresponding to neighbourhood(s) or village(s) with at least one primary health centre. Health centres are supervised by the health zone and can be public or private. Private facilities can be for profit or non-for-profit, if NGO- or faith-based. Patients presenting with severe illness can be referred from health centres to the general referral hospital of the health zone. In Kisantu health zone, health areas Nkandu (urban, more densely populated; 2019 estimated population 26 876) and Kavuaya (peri-urban, less densely populated; 2019 estimated pop. 7617) were selected (Supplementary material). In Kimpese health zone, health areas Malanga (rural, nonetheless on the national road N1 to Kinshasa; 2019 estimated pop. 5431) and Viaza (rural, more remote; 2020 estimated pop. 3788) were selected, both part of an existing health demographic surveillance system (HDSS), in which demographic and health-related indicators are collected during regular household visits.

Study design

We conducted a household survey to estimate the population's rate of healthcare visits by type of provider, and a healthcare visit exit survey to estimate the prevalence of antibiotic use per healthcare visit. We then combined both measures to estimate community-wide antibiotic use.

Healthcare utilisation household survey

In Kisantu, we used a prior healthcare utilisation household survey from March 2019, part of a study measuring the incidence of typhoid fever[15]. Stratified spatial sampling was used to randomly select households, nearest to the randomly generated GPS points within the selected health areas, as primary sampling unit. Where several households were identified within a selected structure, the first household located on the right side in the structure was approached. 645 households per health area were randomly selected. Healthcare visits and self-treatment, not involving a healthcare visit, during the past three months were recorded of all household members, using a paper-based structured questionnaire. In Kimpese, an electronic questionnaire was added to the HDSS round during February-June 2020, recording every community member's healthcare visits in the past three

months. By conducting the surveys in the same months of the year, seasonal differences in healthcare utilisation between both sites were accounted for.

Healthcare visit exit surveys

In a preceding qualitative study, we identified all healthcare providers and provider types in the four selected health areas, through semi-structured in-depth interviews with a convenience sample of formal and informal healthcare providers and patients (Heyerdahl, in preparation). We selected three providers of each of the following healthcare provider types per health area: primary health centres, medicine stores (including private community pharmacies with qualified dispensers and informal stores, as most were in the grey zone in between both), private clinics, traditional healers, and religious leaders – which could sometimes be consulted for medical advice or care. Consecutively presenting patients of any age (or caretakers if aged below 18 years of age) were requested to participate in a healthcare visit exit survey after completing their healthcare visit. When a patient survey was completed, the next patient finishing a visit was selected for the survey. This continued until all visits that day were done. We aimed to interview at least 50 patients who used an antibiotic per provider type per health area, to obtain 95% confidence interval limits of 10% of the proportions of antibiotic groups. If in a selected health area, less than three providers of a provider type existed or agreed to participate, the number of healthcare visit exit surveys to be conducted was equally distributed between available providers. In addition, in the general referral hospital in Kisantu, twice all patients admitted in the hospital were interviewed, recording antibiotic use in the previous 24 hours and treatment duration, with one week in between both rounds. Because certain providers had few patient visits per day, the number of exit surveys could remain under the sample size target.

Using an electronic questionnaire, any patient, or caretaker of paediatric patients, was asked about antibiotics for systemic use dispensed/purchased (generic name), number of units (tablet, capsule, vial, bottle) per treatment course, dose, route of administration, intake frequency, duration of treatment, the patient's age and date of symptom onset. Surveys were conducted in Kisantu in October 2019 and in Kimpese in January 2020.

Data analysis

We estimated the monthly rate of healthcare utilisation by provider type by area, allowing a finite population correction to account for the fraction of residents sampled from the total population within each area and a potential cluster effect within households, using the 'survey' package in R. We inferred the rate by health zone and for both health zones combined, using population weights npopulation_of_area /nstudy_opulation_of_area. The overall rate is the sum of provider type-specific rates.

We estimated the prevalence of antibiotic use, the distribution of antibiotics used by AWaRe (Access/Watch/Reserve) group[16] and by antibiotic class, the distribution of routes of administration, the mean number of Defined Daily Doses (DDD) and median duration of treatment, by healthcare provider type and area. We again used population weights to extrapolate to the health zone and to both health zones combined.

We multiplied the provider type and health zone-specific antibiotic use indicators (prevalence, prevalence of Watch antibiotics, DDD) with the monthly healthcare utilisation rate of that provider type in that health zone, to estimate the monthly community-wide rate of antibiotic use and the DDD used per 1000 inhabitants per day (DID), of any antibiotic and of Watch group antibiotics. Because we could not conduct patient surveys in the Kimpese hospital, we used the antibiotic use indicators from the Kisantu hospital instead when estimating the community-wide rate of antibiotic use in Kimpese.

We also estimated median number of days between symptom onset and healthcare visit and the age distribution of patients from the visit exit surveys.

Ethical considerations

The study protocol was approved by the ITM institutional review board (ref. 1333/19) and the Université Protestante du Congo ethics committee (ref. CEUPC0060). Study participants provided written informed consent: patient or caretaker for healthcare exit survey and household head for healthcare utilisation.

Results

Frequency and timing of healthcare visits

During 2447 household visits (552 in Kisantu, 1850 in Kimpese) healthcare utilisation of 10407 individuals was recorded (3185 in Kisantu, 7222 in Kimpese). The mean age of participants who sought healthcare was 23.6 years in Kisantu, 22.5 years in Kimpese. In Kisantu, 14.5% were under 5 years old; in Kimpese 29.9%.

Combined, 88.7 healthcare visits and 58.0 episodes of self-treatment were reported per 1000 person-months. Private clinics and health centres were the most frequently visited providers (Table 1). The overall healthcare utilisation rate in Kisantu was fourfold that in Kimpese. For the age-specific distribution of healthcare utilisation, see web-only Supplementary Figure S2.

Table 1. Rate of healthcare utilisation by provider type and health area

Type of provider	Monthly healthcare visits per 1000 person-months (95% confidence intervals)		
	Kisantu	**Kimpese**	**Combined**
Hospital	1.26 (0.256-2.24)	1.15 (0.55-1.75)	1.20 (1.02-1.38)
Health centre	27.8 (21.5-34.1)	18.8 (16.4-21.2)	25.5 (24.6-26.4)
Private clinic	38.6 (31.4-45.7)	1.23 (0.61-1.85)	31.0 (30.0-32.0)
Medicine store	20.9 (15.1-26.8)	5.09 (3.82-6.35)	17.6 (16.9-18.3)
Traditional healer	16.5 (12.1-21.1)	1.39 (0.73-2.06)	13.4 (12.8-14.0)
Religious leader*	NA	0.16 (0.00-0.39)	0.07 (0.03-0.16)
OVERALL	105 (94.2-116)	27.8 (24.8-30.8)	88.7 (81.9-95.4)
Selftreatment[#]	58.0 (49.4-66.6)	NA	58.0 (49.4-66.6)

*Visits to religious leaders were not recorded in Kisantu; NA = not applicable

[#] Selftreatment: use of medicines for an episode of illness non involving a healthcare visit. Not recorded in Kimpese.

Patients visited health centres and private clinic median 3 days after symptom onset (both IQR 2-6 days), and medicine stores after median 2 days (IQR 1-4). Hospital admissions (median 9 days IQR 6-14) and visits to traditional healers (median 9 days IQR 5-15) were later (Supplementary Figure S3).

Antibiotic use during healthcare visits

From 2022 healthcare visit exit surveys (1375 in Kisantu and 647 in Kimpese), the population-weighted prevalence of antibiotic use was 74.7% (95%CI 70.5-78.9%, n=412) among hospital-admitted patients, 64.3% (95%CI 55.2-73.5%, n=224) at private clinics, 51.1% (95%CI 45.1-57.2%, n=469) at health centres, and 48.8% (95%CI 44.4-53.2%, n=850) at medicine stores. The prevalence of antibiotic use differed importantly between health zones: at health centres 54.8% (95%CI 47.3-62.3%, n=255) in Kisantu versus 37.4% (95%CI 30.7-44.0%, n=214) in Kimpese; at medicine stores 56.0% (95%CI 50.5-61.4%, n=454) in Kisantu versus 21.9% (95%CI 17.9-26.0%, n=396) in Kimpese (Figure 1). The fraction of Watch antibiotics was higher in private clinics (30.3%, 95%CI 24.6-35.9%) than health centres (25.1%, 95%CI 19.0-31.2%) or medicine stores (25.6%, 95%CI

20.2-31.1%). No antibiotics of the Reserve group or not on the 2021 WHO Essential Medicines List were reported.

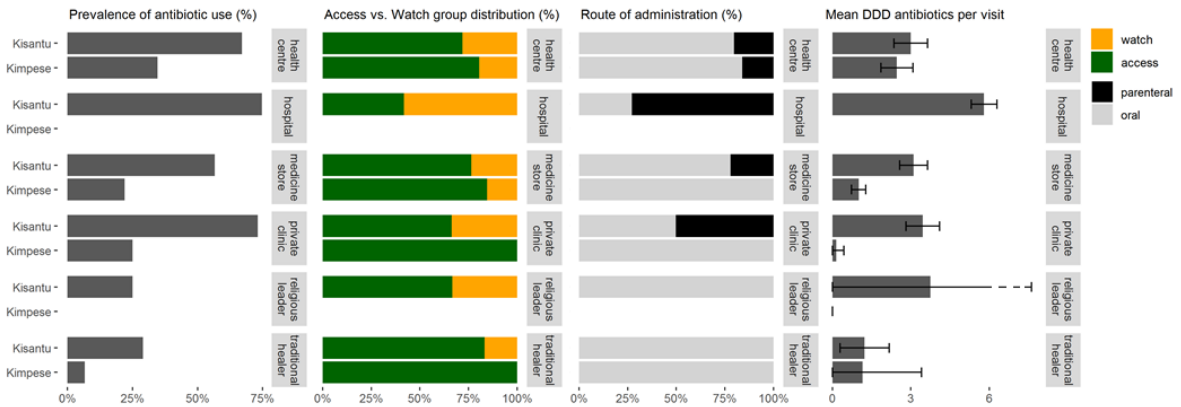

Figure 1. The prevalence of antibiotic use (among all visits), the distribution of AWaRe groups among antibiotics used, the distribution of routes of administration, and the mean number of defined daily doses of antibiotic used during/following one healthcare visit, by health zone. The 95% confidence interval of mean DDD during visits to religious leaders in Kisantu was -3.6-11.1.

Parental use of antibiotics was more frequent in private clinics (46.3%, 95%CI 38.1-54.4%) than health centres (15.4% 95%CI 10.3-20.4%). The mean defined daily doses of antibiotic used per visit were comparable between health centres (2.9 DDD, 95%CI 2.4-3.4), private clinics (2.8 DDD, 95%CI 2.3-3.3), and medicine stores (2.7 DDD, 95%CI 2.2-3.1).

The median duration of treatment was 7 days (IQR 5-7) at health centres and 5 days (IQR 5-7) at private clinics (p<0.01). It was 7 days (IQR 5-7) at traditional healers and 5 days (IQR 5-7) at medicine stores. Duration of treatment <3 days was more frequent at private clinics (5.3%, 9/169) and medicine stores (4.1%, 14/338) than at primary health centres (1.8%, 5/277, p=0.05 and p=0.04 respectively).

Community-wide antibiotic use

Antibiotics were used during the previous month by 6.2% (95%CI 4.4-8.9%) of the population in Kisantu and 0.81% (95%CI 0.46-1.2%) in Kimpese. The overall antibiotic use was 10.2 DID (95%CI 6.00-15.4 DID) in Kisantu and 1.75 DID (95%CI 1.02-2.39 DID) in Kimpese (Supplementary Figure S4). Most of this gap is explained by differences in healthcare utilisation: in Kisantu overall fourfold higher and more frequent visits to private clinics, where antibiotic use was higher (Figure 1). Visits to private healthcare providers accounted for 70.8% of DID in Kisantu and 13.0% of DID in Kimpese. The overall Watch group antibiotic use was 3.25 DID (95%CI 1.48-5.60 DID) in Kisantu and 0.37 DID (95%CI 0.15-0.64 DID) in Kimpese.

Choice of antibiotics

Community-wide, the most frequently used antibiotic classes were penicillins (49.5%, 95%CI 46.7-52.3%), cephalosporins (14.2%, 95%CI 12.3-16.2%), nitroheterocyclics (12.1%, 10.3-14.0%, mainly metronidazole), fluoroquinolones (7.1%, 95%CI 5.7-8.5%) and macrolides (6.4%, 95%CI 5.1-7.8%). Cephalosporins were more frequently used in private clinics (25.3%, 95%CI 18.8-31.7%) than medicine stores (11.8%, 95%CI 8.5-15.1%) or health centres (9.3%, 95%CI 5.9-12.7%). Fluoroquinolones were more frequently used in medicine stores (9.0%, 95%CI 6.1-12.0%) and health centres (7.0%, 95%CI 4.0-10.0%) than private clinics (5.1%, 95%CI 1.8-8.3%).

Supplementary Tables provide the distribution of antibiotic classes among <5 year olds and of individual antibiotics.

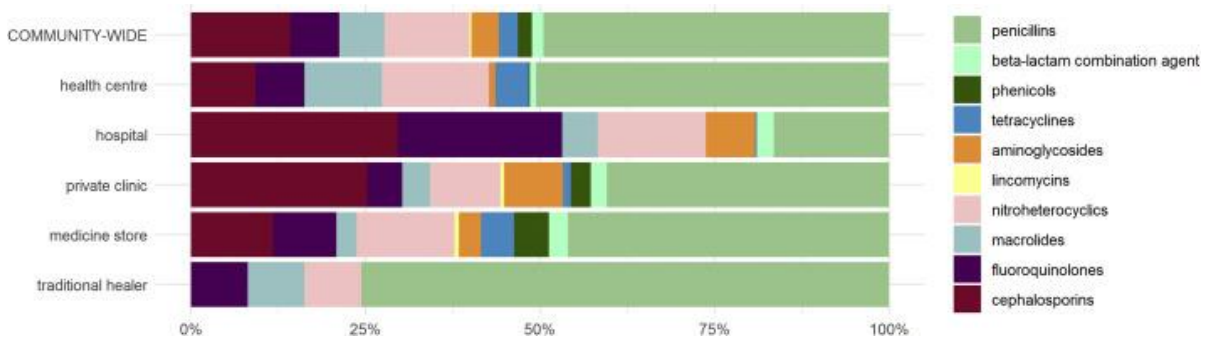

Figure 2. Antibiotic class distribution of antibiotic courses used, by type of healthcare provider and community-wide, combining Kimpese and Kisantu health zones by weighting for population size and the provider-specific healthcare utilisation rate.

Discussion

Over 50% of community-wide antibiotic use resulted from visits to private healthcare providers, though their share was higher in urban Kisantu than in rural Kimpese. Private providers not only dispensed antibiotics more frequently, treatment courses consisted more frequently of Watch antibiotics and were more frequently shortened. Only 3% of community-wide antibiotic use resulted from the hospital, owing to infrequent hospital admissions.

Antibiotic use in Kisantu (10.2 DID) was comparable to lower middle-income countries (median 10.8 DID), and that of Kimpese (1.75 DID) was lower than that in any country in a 2015 study of 76 high- and middle-income countries [14]. In both sites, antibiotic use was importantly lower than in most European countries (mean 20.0 DID, range 8.9-34.1 DID), emphasizing the lack of access to appropriate antibiotic treatment, or to healthcare in general [17,18]. The prevalence of antibiotic use during health centre visits (51.1%) was similar, and that during private clinic visits (64.3%) was higher, than the pooled prevalence during primary care centre visits (52%) estimated in a systematic review in 27 LMICs [19]. Hence, low community-wide antibiotic use can rather be explained by infrequent healthcare seeking, owing to poor access to healthcare. That could also explain the difference between both study health zones despite their geographical proximity. Socio-economic and health system differences determine health care frequency (in peri-urban Kisantu fourfold that in rural Kimpese) and to a lesser extent to the prevalence of antibiotic use per visit (in Kisantu nearly twofold that in Kimpese). In Kisantu, medicine stores and clinics are widely present, with different types of medicine stores for every budget or illness. In its official healthcare facilities, a flat rate per consultation or hospital admission is applied. Kimpese is probably more similar to most zones in DRC, with difficult access to health care and exclusively out-of-pocket payments, curtailing timely consultation and treatment.

Considering the increasing prevalence of bacterial resistance against Watch antibiotics[5,6], we were particularly interested in the use of Watch antibiotics. The fraction of Watch antibiotics (31.9% of DID in Kisantu, 21.1% in Kimpese) was lower than that observed in most countries with data available (worldwide 38.6%)[14]. Watch antibiotic use was higher in urban health areas, explained by their frequent use in private clinics and over-the-counter in medicine stores.

Combining two surveys, we measured antibiotic use in settings where antibiotic use cannot be routinely estimated from sales data or medical records, and where healthcare and medicines are in large part offered by an unregulated private sector. The inclusion of all healthcare providers types

and the random sampling of households provided unique healthcare utilisation data that standalone provider-based antibiotic use surveys cannot offer. Healthcare visit exit surveys could be regularly repeated in a number of sentinel sites where population healthcare utilisation data is available, offering a feasible way to monitor trends in antibiotic use and measure the effectiveness of efforts to optimize antibiotic use.

Study limitations: Antibiotic use could be underestimated as a result of difficulties recalling visits during healthcare utilisation surveys. The predefined number of healthcare visit exit surveys at traditional healers and religious leaders was not attained because of infrequent patient visits, limiting comparisons of their indictors. The appropriateness of the antibiotic courses used cannot be assessed from patient visit exit surveys without full anamnesis and clinical/diagnostic examination. Our findings underscore widely differing antibiotic use between two geographically close areas, hence, cannot draw any conclusions on nation-wide antibiotic use.

The surprisingly high antibiotic resistance prevalence among bloodstream infections in DRC, of chiefly community-acquired pathogens[5,6], could be the result of an interaction between poorly controlled bacterial infections, and frequent exposure of these bacteria to antibiotics. Both factors relate to difficulties accessing appropriate diagnostic capacity and resulting self-medication with (underdosed) antibiotics from private providers. Optimizing antibiotic use also involves ensuring sufficient access to the appropriate antibiotic treatment[18].

Antibiotic dispensing by private providers is not overseen by health authorities, nor are we aware of existing antibiotic stewardship interventions targeting private providers those in DRC or elsewhere in Central Africa. Intervention bundles to optimize antibiotic use, including training of medicine store staff and other community-level providers, have shown to improve clinical care and in some occasions to decrease antibiotic use[20,21], and should be considered on a wider scale, albeit adapted to the local health care landscape.

Author contributions

BI, PM and MABvdS designed the study; BI, DMP, MFP, MYNB, FKK, LK, BM, JI, LH and OL collected the data and contributed to writing; FKK and LH provided insights from the preceding qualitative study in questionnaire design and interpretation; BI and NMB verified, curated and analyzed the data; BI, RIDL, MJMB, OL, JJ and MABvdS interpreted the results and contributed to the writing; all authors critically reviewed and contributed revisions to the final version of the paper. We would like to thank Esther Van Kleef for reviewing statistics used in a revision of the manuscript.

Transparency declaration

All authors declare no competing interests. This work was part of the Bacterial Infections in the Tropics research cluster at the Institute of Tropical Medicine, funded by the InBev-Baillet-Latour Fund. Kimpese Health Research Center and Institut National de Recherche Biomédicale, Democratic Republic of Congo, received funding by the Belgian Directorate of Development Cooperation for Antimicrobial Resistance projects. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data access

Pseudonymized individual data collected for the study, study protocol, questionnaires, and analysis scripts are available on https://github.com/ingelbeen/cabu

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Supplementary data

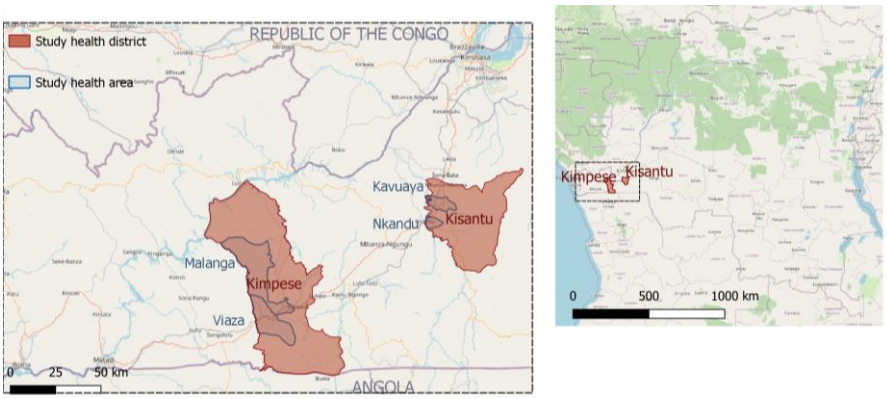

Figure S1. Study sites. In red the health zones, in blue the selected health areas

Table S1. Healthcare visits per 1000 person-months (95% confidence intervals) by health area

Type of provider	Healthcare visits per 1000 person-months (95% confidence intervals)				
	Kisantu		Kimpese		Combined
	Nkandu	Kavuaya	Viaza	Malanga	
Hospital	1.60 (0.33-2.88)	0	1.15 (0.55-1.75)	0.528 (0.07-0.99)	1.20 (1.02-1.38)
Health centre	21.1 (14.8-27.4)	51.4 (33.5-69.2)	18.8 (16.4-21.2)	15.6 (13.1-18.1)	25.5 (24.6-26.4)
Private clinic	41.1 (32.7-49.6)	29.6 (13.3-43.8)	1.23 (0.61-1.85)	3.59 (2.38-4.80)	31.0 (30.0-32.0)
Medicine store	18.8 (12.6-25.0)	28.6 (13.2-44.0)	5.09 (3.82-6.35)	4.75 (3.36-6.14)	17.6 (16.9-18.3)
Traditional healer	13.7 (9.36-18.1)	26.6 (13.1-40.0)	1.39 (0.73-2.06)	1.48 (0.70-2.25)	13.4 (12.8-14.0)
Religious leader	NA	NA	0.16 (0.00-0.39)	0	0.07 (0.03-0.16)
OVERALL	96.4 (84.4-108)	136 (109-163)	27.8 (24.8-30.8)	26 (23-29)	88.7 (81.9-95.4)
Selftreatment	62.2 (52.1-72.3)	43.1 (27.5-58.7)	NA	NA	53.4 (44.3-62.5)

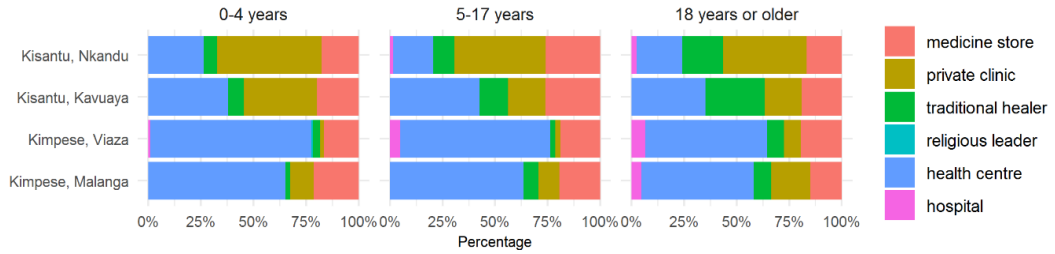

Figure S2. Distribution of healthcare utilisation by provider type, age and health area

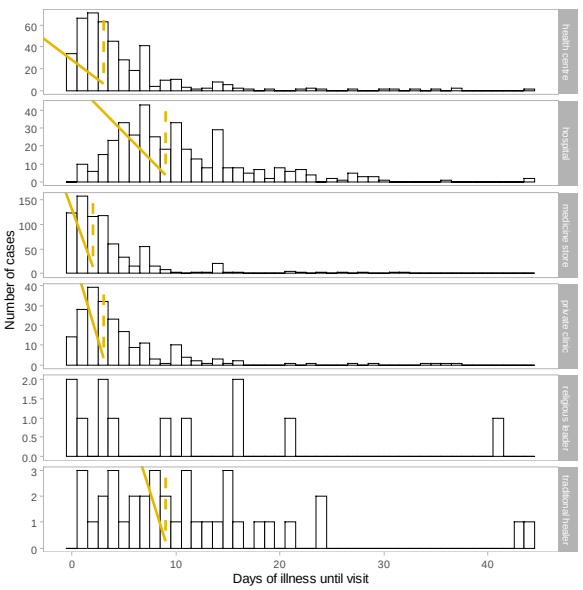

Figure S3. Days between symptom onset and visit to a healthcare provider, by type of provider. Dashed yellow line is the median (none provided for religious leaders)

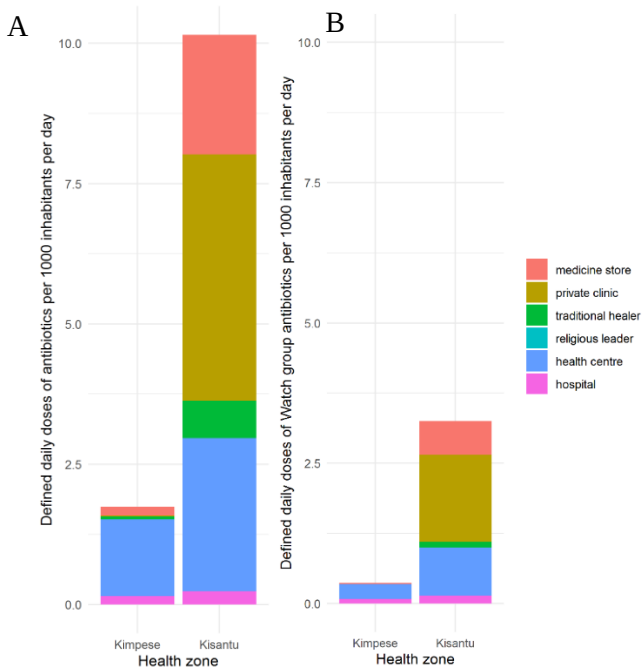

Figure S4. Bar chart with Defined daily doses of antibiotics (A) or of Watch group antibiotics (B) per 1000 inhabitants per day (DID), by health area and by provider type

Table S2. Antibiotic class distribution of antibiotic courses by type of healthcare provider, combined for Kimpese and Kisantu health zones by weighting for population size and healthcare utilisation rate

Antibiotic class	health centre			hospital			medicine store			private clinic			COMMUNITY-WIDE		
	%	95%CI		%	95%CI		%	95%CI		%	95%CI		%	95%CI	
All ages															
penicillins	50.54	44.68	56.41	16.50	12.92	20.09	45.98	40.81	51.15	40.41	33.16	47.66	49.48	46.69	52.26
cephalosporins	9.28	5.88	12.68	29.61	25.20	34.02	11.79	8.45	15.14	25.26	18.84	31.68	14.21	12.27	16.16
nitroheterocyclics	15.30	11.07	19.52	15.53	12.04	19.03	14.00	10.40	17.60	10.10	5.65	14.55	12.14	10.32	13.96
fluoroquinolones	6.98	3.99	9.98	23.54	19.45	27.64	9.04	6.07	12.02	5.05	1.82	8.29	7.08	5.65	8.50
macrolides	11.11	7.42	14.79	5.10	2.97	7.22	2.90	1.16	4.64	3.93	1.06	6.80	6.44	5.08	7.81
aminoglycosides	0.93	-0.20	2.06	7.04	4.57	9.51	3.10	1.30	4.90	8.42	4.32	12.52	3.92	2.84	5.00
tetracyclines	4.80	2.29	7.31	0.24	-0.23	0.72	4.76	2.55	6.97	1.12	-0.43	2.68	2.73	1.82	3.63
phenicols	0.16	-0.31	0.63	0.00	0.00	0.00	4.97	2.72	7.23	2.81	0.37	5.25	2.02	1.23	2.80
beta-lactam combin.	0.90	-0.21	2.00	2.43	0.94	3.91	2.76	1.06	4.46	2.34	0.11	4.58	1.65	0.94	2.37
lincomycins	0.00	0.00	0.00	0.00	0.00	0.00	0.69	-0.17	1.55	0.56	-0.54	1.66	0.33	0.01	0.66
Patients under 5 years old															
penicillins	43.87	34.92	52.82	10.20	4.21	16.20	39.10	29.02	49.19	44.07	33.12	55.02	41.05	36.16	45.95
cephalosporins	5.12	1.14	9.10	62.24	52.65	71.84	18.01	10.07	25.95	27.70	17.83	37.57	15.53	11.92	19.13
nitroheterocyclics	25.61	17.73	33.48	3.06	-0.35	6.47	16.37	8.73	24.01	8.81	2.56	15.07	13.81	10.37	17.24
macrolides	14.54	8.18	20.91	5.10	0.75	9.46	8.46	2.71	14.22	5.04	0.21	9.86	12.66	9.35	15.97
fluoroquinolones	9.43	4.15	14.70	15.31	8.18	22.43	6.58	1.45	11.70	1.26	-1.20	3.72	9.59	6.66	12.52
aminoglycosides	0.00	0.00	0.00	4.08	0.16	8.00	5.46	0.76	10.15	5.04	0.21	9.86	2.91	1.24	4.58
phenicols	0.41	-0.74	1.57	0.00	0.00	0.00	1.92	-0.91	4.76	6.30	0.94	11.65	2.72	1.10	4.34
beta-lactam combin.	1.02	-0.79	2.84	0.00	0.00	0.00	4.09	0.00	8.19	1.78	-1.14	4.70	1.74	0.44	3.04

Page 110-111: Distribution of houses struck by cholera ("... maisons où le Cholera a sevi...") during the 1866 cholera outbreak, Antwerp. Copyright Stadsarchief Antwerpen.

Ville d'Anvers.

Bureau de l'Ingénieur.

lan indiquant par une teinte noire maisons où le Choléra a sévi pendant l'épidémie de 1866.

1ère Feuille.

Dressé par l'Ingénieur de la Ville soussigné.
Anvers, le 22 Janvier 1867.

9- General discussion

Opportunities and gaps of existing surveillance systems for infectious disease outbreaks

Over the course of large infectious disease outbreaks – most outbreaks situated in low- and middle income countries (LMIC) – facility-based notifiable disease reporting, from health centres, hospitals, laboratories, or treatment/isolation wards have been pivotal even though limited by delays (from disease progression until health care seeking, diagnosis, and reporting) and underreporting (from healthcare seeking that is avoided or at private or informal providers) - as illustrated in chapters 3 to 8 and in Table 1. Moreover, lacking diagnostic capacity to confirm cases in primary care and delayed reporting, analysis, and interpretation of surveillance data further impact the timeliness of infectious disease control informed by facility-based case/death reporting. The window for effective outbreak containment has in some cases passed.

Table 1. Selected infectious disease outbreaks during 2013-22 and surveillance systems involved

Outbreak	Features
Ebola 2013-16, West-Africa (overall 28646 cases 11323 deaths; Guinea 3811 cases 2543 deaths)	**Surveillance system(s):** Daily case and death counts from treatment/isolation centre line list and reported community deaths; Daily contacts traced/followed-up/missed **Control intervention(s):** Isolation in treatment centres with PCR testing of suspected cases; Community sensitisation; Engage survivors to overcome barriers of testing and isolation; Contact tracing with (twice) daily temperature monitoring; Ring vaccination with rVSV-Zaire Ebolavirus vaccine; Triage at healthcare facilities with point-of-care PCR testing; Infection prevention and control (e.g. handwashing) **Response trigger:** First confirmed EVD case **Limitations:** Delayed isolation of symptomatic patients due to limited access to healthcare, fear, mistrust and negative perceptions of the quality of EVD care; Absence or overwhelmed contact tracing, resulting in late isolation of infected contacts; Shortage of qualified and paid public health workforce **Unique/innovative:** Point-of-care PCR confirmatory testing of suspect cases; Role of survivors in removing stigma of treatment/isolation centers
Yellow Fever 2015-16, Central-Africa (overall 954 confirmed cases 137 deaths; in DR Congo alone 70 confirmed cases 16 deaths)	**Surveillance system(s):** Laboratory confirmations of suspected cases referred to centralised treatment centres **Control intervention(s):** Active case finding and isolation; Vaccination with fractioned Yellow Fever vaccine doses; Community sensitization to promote vector control and health care seeking; Free care for confirmed cases **Limitations:** Absence of timely vector control and public health messaging; Delayed isolation of infected persons due to absence of absence of testing and low sensitivity of case definition to detect early cases; Absence of qualified and paid public health workforce **Response trigger:** Local transmission (human > mosquito > human) in densely populated areas with presence of vector (A. albopictus) **Unique/innovative:** Reinforced vector control and sensitization in a radius of 200m around cases' residences; Vaccination with fractional-doses of the YF vaccine
Cholera 2008-17, DR Congo (66008 suspected cases, 5231 deaths)	**Surveillance system(s):** Weekly facility-based case reporting; National reference laboratory **Control intervention(s):** Isolation of cases; Free care; Promote healthcare seeking and hygiene practices; Water treatment at wells; Oral Cholera Vaccine campaigns **Limitations:** Little use of surveillance data for early detection or predicting geographical spread of outbreaks, or to plan or target control measures; Limited use of Oral Cholera Vaccine; No or few studies to identify sources of outbreaks **Response trigger:** Non-endemic areas: Single confirmed case or increase in weekly number of syndromic cases or deaths; Endemic areas: sustained increase in weekly number of syndromic cases or deaths **Unique/innovative:** Oral cholera vaccine campaign in cholera hotspots based on endemicity
Antibiotic resistant bacterial infections, DRC	AMR surveillance **Surveillance system(s):** Laboratory reporting of bloodstream infection cases: identified species and antibiotic susceptibility testing, providing prevalence of resistance among specific pathogen-antibiotic combinations

(In Central Sub-Saharan Africa in 2019 estimated 27200 deaths attributed to bacterial AMR)	**Control intervention(s):** Adapted hospital antibiotic treatment protocol for suspected bloodstream infections; Typhoid conjugate vaccine among young 6 months to 5 year olds **Limitations:** Limited access and utilization of public health care resulting in selection bias; Adherence to hospital treatment guidelines; Absence of AMR awareness and knowledge **Response trigger:** Increase in pathogen-antibiotic-specific AMR prevalence; Increase in confirmed AMR bloodstream infection cases **Unique/innovative:** Introduction of Typhoid conjugate vaccine Antibiotic use surveillance **Surveillance system(s):** Repeated point-prevalence surveys in hospitals; repeated community-wide antibiotic use estimated from sales data or patient visit exit surveys **Control intervention(s):** Adapted hospital antibiotic treatment protocol for suspected bloodstream infections; Adapting standard treatment guidelines; Antibiotic stewardship programs; Community and healthcare worker sensitization **Limitations:** Absence of diagnostic tools to confirm or distinguish bacterial infection at primary care before starting antibiotic treatment; Absence of treatment guidelines; Resource-demanding for interventions with often no direct visible clinical benefit **Response trigger:** Increase in pathogen-antibiotic-specific AMR prevalence; Increase in confirmed AMR bloodstream infection cases **Unique/innovative**: Antibiotic use surveillance in absence of sales data
COVID-19 2019-22, Mozambique (225519 confirmed cases; 2201 deaths*; 42728 estimated excess deaths**)	**Surveillance system(s):** National reference laboratory (network) case reporting; repeated sero-surveys **Control intervention(s):** COVID-19 vaccination; Test, isolate and trace, with testing and quarantine of contacts; Physical distancing measures; Masks; Travel restrictions **Limitations:** Underreporting (limited testing, narrow case definition); limited access to healthcare and testing delaying timely isolation and quarantine of contacts; limited contact tracing capacity; vaccine hesitancy **Response trigger:** Sustained local transmission **Unique/innovative:** Use of rapid antigen tests in test streets; Generalised physical distancing measures; Repeated sero-surveys

EVD, Ebola Virus Disease; AMR, Antimicrobial resistance; * As of 18 May 2022; **World Health Organization Global excess deaths associated with COVID-19 (modelled estimates), https://www.who.int/data/sets/global-excess-deaths-associated-with-COVID-19-modelled-estimates, data of 5 May 2022.

I explore options to improve timeliness of infectious disease control in low-resource settings, in LMIC but also areas or populations in high-income countries which are neglected in terms of public health, preparedness, and disease prevention and control.

Improve timely case detection

Adapting case definitions during an outbreak could already help overcome the delay from disease progression, as illustrated by the Yellow Fever outbreak in chapter 3. Case definitions are generally static, not regularly adapted to changing transmission dynamics or taking into account new geographical foci. Nevertheless, as with Ebola in chapter 2, Yellow Fever in chapter 3, or cholera in chapter 4, the pathogen might be spreading in geographically limited areas where case patients rarely move out when ill or the vector transmitting the pathogen is present, and these geographical foci might be changing during the outbreak. Integrating the latest epidemiological case data, such as spatial clustering of cases and patient's mobility history, could improve case definition's diagnostic performance. Yet it would require real-time availability of these data in order to regularly update the epidemiological criteria of the case definition, and ideally come through electronic connected devices that help healthcare workers assessing whether patients meet the case definition at that time.

Decentralised, accessible, affordable, and rapid testing with a single and well performing diagnostic test is the holy grail of outbreak response. Especially in primary care and in low-resource settings,

a lack of diagnostic capacity limits surveillance of endemic and emerging infectious diseases. Diagnostic tests for endemic diseases, if available, often require out-of-pocket payment from patients, and their use is therefore suboptimal. Moreover, few new diagnostic tools are adapted to healthcare facilities with limited resources (1). An exception here was the introduction of Xpert MTB/RIF point-of-care PCR assay to diagnose tuberculosis and simultaneously detect rifampicin resistance in countries with a high tuberculosis burden, following a recommendation by the World Health Organization (WHO) in 2010. It has speed up the identification of tuberculosis cases and improved sensitivity, even though the long-term effect on mortality remains contested (2,3). Already by 2016, the platform was used for diagnostic tests other than tuberculosis in 37% of the high tuberculosis burden countries (4). Nevertheless, the price per test has not gone down – against the expectation that implementation in two dozen countries would lead to economies of scale reflected in lower prices. With competition from other companies commercialising such platform still absent, it's not certain prices will eventually drop to a level that permits point-of-care testing financed by out-of-pocket payments from patients (5). Still, it has proven that advanced diagnostic testing is also feasible outside tertiary care facilities or to the industrialised world. Apart from the availability of the diagnostic test, its implementation is crucial as well. Chapter 2 illustrated how delays in sample collection, testing and reporting affected Ebola outbreak response, adding an additional barrier to sick, potential cases getting tested and isolated, and delaying appropriate care for suspected cases who turned out not to be infected with Ebolavirus. Immediate testing in the treatment centre shortened that delay, and substituting the second test required for some patients by home isolation, follow-up of symptoms and testing at-home, could further lift the barrier of seeking a test to exclude an infection when ill.

Surveillance of risk, rather than of disease

Rather than waiting for changes in disease progression, monitoring changes in risk allows to take preventive or control measures before or at the start of an outbreak, and to focus measures on the specific change in risk underlying an imminent outbreak. During spring 2022, vaccine derived poliovirus type 2 was repeatedly detected in sewage surveillance in the United Kingdom (14). Using polio vaccination data, subpopulations with low vaccination coverage were identified and contacted for catch-up vaccination. Hence, the risk of an outbreak was mitigated even before a first case of disease – in this case paralysis – occurred, with prevention of an outbreak informed by two sources of risk surveillance. Risk can be (i) exposure, such as the aforementioned persisting circulation of vaccine-derived poliovirus in sewage samples, or circumstances that facilitate infectious agents' transmission, (ii) determinants of exposure or of disease progression, such as vaccination coverage below the critical threshold, or pathogen-specific antibody levels, (iii) pre-symptomatic infection or carriage, such as nasopharyngeal carriage surveys to determine the distribution of pneumococcal serotypes and (mis)match with vaccines, or (iv) characteristics of the pathogen, such as AMR genes or of SARS-CoV-2 variants (Figure 1). In LMIC, surveillance of the risk of outbreaks is largely lacking, despite more frequent animal-to-human spillover, zoonoses, food, water- or vector-borne diseases, or AMR disease outbreaks.

Facility-based surveillance reporting cases or deaths can actually provide trends in risk, to inform prevention measures. Historical trends in case or death numbers by area and subpopulation can help prioritise areas or subgroups most at risk of (severe) disease for preventive or early outbreak control measures. In chapter 4, we identified areas in the Democratic Republic Congo (DRC) at elevated risk of recurring cholera outbreaks every few years, with high case fatality, that should be prioritised for investments in safe drinking water and sanitation or for oral cholera vaccination campaigns before a new outbreak hits. It demonstrated that informing and targeting outbreak prevention and

control can be done using facility-based case and death counts, despite delays, underreporting and poor performing case ascertainment in the absence of laboratory tests.

Similarly, during the COVID-19 pandemic, introducing control measures based on case, reports, hospital admission, or deaths reports, suffered from delays in disease progression, diagnosis and reporting. Yet, surges or waves could be anticipated from the trend in the number of contacts cases reported, as illustrated in chapter 5, offering opportunities to improve timeliness of control measures. Both examples provided however require regular analysis and interpretation of surveillance data, and epidemiological (human resource) capacity dedicated to monitoring threats that are no acute outbreaks at that time.

Granularity of the data is crucial: access to local and not just national surveillance data can facilitate targeting of high-risk geographical foci and subpopulations, to improve the effectiveness and efficiency of interventions. In Niger, monitoring Group A meningococcal meningitis at the level of 'health areas' (median population of 14,440) rather than at the district level (median population of 295,200) improved the sensitivity of detecting new outbreaks, reducing the delay to respond and start vaccination campaigns, halving the number of cases in an outbreak (6).

Generally absent in LMIC, testing for emerging pathogens or testing of environmental or veterinary samples allow the identification of potential threats to human health, to target preventive or early outbreak measures. Even though such surveillance is limited to some industrialised countries, the risk for zoonotic spillover or the emergence of more virulent, transmissible or resistant pathogens is highest in LMIC in South Asia and Sub Saharan Africa (7–11).

Obtain measures of disease occurrence by correcting for healthcare seeking and size of the (sub)population

In many LMIC, healthcare utilisation is shifting away from official facilities to private clinics and pharmacy stores, or self-medication, for a number of reasons: unawareness of the disease and of the importance of early treatment, fear (e.g., for isolation), waiting lines, cost, and (perceived) poor quality of care (12–14). Facility-based surveillance will miss a share of disease cases in the community or will pick them up only later in the course of disease.

To support setting priorities and target interventions to specific subpopulations and areas at risk, measures of disease occurrence and burden are needed: incidence, prevalence, or mortality estimates to start with. These require population denominators and need to be corrected by the proportion of disease cases in the population that are actually diagnosed and reported by health care facilities. Obtaining population denominators can be challenging in LMIC, where birth, death or population registers are not always up-to-date. The proportion of healthcare utilization can be obtained from specific health care utilisation surveys for that purpose, but also from demographic health surveys, censuses, or from community-based surveillance – which we will get to later (15). A caveat here may be changes in healthcare utilisation throughout an outbreak, as this can bias trends (16,17). For example, populations may avoid healthcare seeking out of fear for healthcare associated infections or compulsory admissions with costs associated. Alternatively, healthcare seeking may increase following disease outbreaks if healthcare admissions are offered free of charge.

The absence of population registries, with unique identifiers to link surveillance and population data, not only complicates estimating measures of disease frequency, but also hampers the identification of subpopulations at specific risk of disease. When not possible to track changes in health status of the entire population, geographically limited population cohorts, as in Health and Demographic

Surveillance Systems (HDSS), could link disease surveillance data to demographic, socio-economic, underlying conditions, risk and exposure data. In the next section, I discuss this in more detail.

Integrate antimicrobial resistance (AMR) and antimicrobial use surveillance

Most infectious pathogens can be effectively controlled when susceptible to antimicrobials, so that outbreaks or clusters of cases do not necessarily require outbreak control measures beyond antimicrobial treatment. An AMR pathogen though poses a double threat: difficult treatment, and sustained transmission when infections are no longer cleared and the pathogen can continue to circulate, potentially exchanging AMR genes it carries with other bacterial species in the microbiome or in the environment. Therefore, not only specific outbreaks of an AMR pathogen are of interest. Sporadic cases of a newly emerging or of an existing pathogen-antimicrobial combinations can be equally important. Consequently, AMR surveillance cannot consist only of facility-based disease and death counts. The WHO set up the Global Antimicrobial Resistance and Use Surveillance System (GLASS), which proposes continued surveillance of the prevalence of AMR among selected pathogen-antimicrobial combinations in selected specimen types, continued surveillance of antimicrobial consumption, reporting of emerging AMR, with repeated surveys to determine AMR in animals and point prevalence surveys for antibiotic use in hospitals (18). Systematic surveillance is complemented by research studies reporting specific AMR genes, monitoring AMR in urban sewage, or estimating country-wide antibiotic consumption from medicine sales data (19,20).

Notwithstanding the ambitions of the WHO, in most LMIC, AMR surveillance is still largely limited to clinical testing of the antibiotic susceptibility of pathogens underlying bloodstream infections in few (mostly) tertiary care hospitals, because of its cost and complexity. Access to these hospitals is extremely poor and the sensitivity of bacterial culture can be compromised by antibiotic use prior to sample collection, frequent in LMIC (see chapters 6, 7 and 8). Despite these limitations, AMR bloodstream infection surveillance data can still provide valuable trends over time, guide hospital-based treatment guidelines, and support estimations of the disease burden attributable to AMR – if corrected for its limitations (21).

In chapter 7 and 8, we proposed two surveys to measure and – if repeated – monitor community-level antibiotic use in LMIC where no antibiotic sales data are available. Community-level antibiotic use is a key risk factor for AMR in community-acquired infections. In an interplay with elevated AMR bacterial carriage and transmission, it potentially explains the surprisingly high AMR prevalence in most LMIC (22). If medicine use surveys can be repeated, providing a surveillance system of community-level outpatient antibiotic use, it could guide, target and evaluate interventions to improve antibiotic use in primary care and from medicine stores or community pharmacies, currently largely absent (23).

Data to improve timeliness and effectiveness of prevention/control in low-resource settings

Beyond facility-based case and death counts, alternative and realistic options exist for surveillance systems that can better detect (proxy) signals of infectious disease threats, inform control interventions, or support risk communication to healthcare workers and populations. Balancing between public health burden and the avoidance of excessive costs or overburdening scarce public health capacity on the other, is crucial.

Data from outbreak control interventions

Control interventions such as active case finding, case investigations, screening, contact tracing, routine vaccination, or vaccination campaigns can provide suitable surveillance data. These data are generally more exhaustive than facility-based case reported data. They can provide indicators based

on either disease (increase in cases, human-to-human transmission, case fatality) or on risk (proportion of missed high-risk contacts, vaccination coverage, inappropriate use of Watch antibiotics, number of physical contacts, presence of vectors, bednet uptake, etc.) to target or evaluate interventions, or supporting risk communication (Table 2).

Table 2. Measures of disease or of risk of disease to inform outbreak and AMR control

Disease/risk	Indicator signal	Public health measure	Example
Disease			
Case number	Single possible confirmed case	Investigate outbreak; active case finding; population screening	Ebola virus disease; rabies; sleeping sickness
	Increase (in incidence/ prevalence)	Targeted sensitization and health education on risk; risk group screening; vaccination	HIV; Hepatitis C Meningococcal meningitis
	Reaching health care capacity		Influenza, chikungunya
Transmission	Human-to-human transmission	Contact tracing and quarantine, isolation, ring vaccination	New pathogen, SARS-CoV-2, monkeypox virus
	Cluster of linked cases, belonging to the same genomic clade	Outbreak investigation, link to common event or source	Food-borne outbreak identified from sequencing of isolates
	Time since last reported case	Contact tracing, vector control	Yellow Fever DRC; Ebola West Africa/DRC
	Sustained transmission	Increasing hospital capacity; social distancing measures	COVID-19
Death number	Single possible death (e.g., adult death following dehydration)	Start investigation; confirmatory test; search cases	Cholera
	Single confirmed death	Set-up isolation and treatment facilities	
	Case fatality above a threshold	Vaccination; Free healthcare (reduce healthcare seeking delay)	Cholera
Environmental or animal			
Vector	Presence of specific vector (e.g., Aedes aegypti) Increase in number of breeding sites	Vector control; sensitization and health education; strengthen disease surveillance	Yellow Fever; dengue
Sewage	Quantifying AMR genes Increase in presence of (AMR) infectious agent	Early warning to scale up testing or search for cases	COVID-19; ESBL-producing Enterobacterales; norovirus
Vulnerability	Refugee camp	Repeated vaccination campaigns	measles, cholera, diphtheria, polio
	Flooding	Provide access to safe water	cholera
Food	Selected pathogen identified in food sample Safety indicator organisms in food sample		
	Pathogens from human cases belonging to the same genomic clade	Outbreak investigation, link to common food source	
	Animal outbreak of pathogen relevant for human or animal health		Q fever, Anthrax
WASH	% access to safe drinking water % households with latrine		Bacterial AMR, Cholera
Population/host factors			
Susceptibility	Malnutrition	Programs supporting food security and biodiversity in agriculture	Invasive non-Typhi Salmonella
	Maternal immunity vs. T. gondii	Prenatal serological screening	Congenital toxoplasmosis
Comorbidity	HIV infection	Isoniazid preventive therapy; Trimethoprim/sulfamethoxazole prophylaxis	Tuberculosis; Pneumocystis carinii pneumonia
Risk of spread	Qualitative assessment	Reinforced contact tracing	COVID-19 in France
Behavioural			
Population mobility	Imported cases estimated from the number of air passengers coming in from a location	Passenger quarantaine; travel restrictions; pre-travel tests	Ebola virus disease; COVID-19 Influenza pandemic
	Frequented places (e.g. home, work, school)	Target interventions to place where exposure is highest	Dengue, Yellow Fever, COVID-19
Social mixing	Number of direct/indirect contacts	Physical distancing measures School closures	COVID-19 Influenza pandemic
(Inappropriate) antibiotic use	Defined daily doses per capita Access-to-Watch index	Restrict use of antibiotics; antibiotic stewardship programs; treatment guidelines	Bacterial AMR

	Prevalence of Self-Medication with Antibiotics		
Sexual attitudes*	Number of sexual partners (in 12 last months) Condom use at the last intercourse for stable, casual and paid partners Experience of HIV testing**	Targeted sensitization and health education on risk; risk group screening	Hepatitis C; HIV
	Increase in cases during outbreak among sex having sex with men	Outbreak investigation; Targeted sensitization and health education on risk; risk group screening	Hepatitis C; Monkeypox; HIV
Intravenous drug use	Self-reporting during population-based surveys or by blood donors	Needle and syringe (exchange) programmes	Hepatitis B & C; HIV
Programmatic			
Vaccination coverage	Under threshold for population immunity	Vaccination campaigns; Catchup vaccination	Measles; Diphtheria
Infection Prevention and Control	Handwashing compliance	Sensitization; Access to water infrastructure programs	MRSA; Klebsiella spp.; Acinetobacter baumanii
Bed net use	Under threshold to stop transmission	Bednet distribution; Sensitization	Malaria; dengue fever; Yellow Fever; Zika virus; Chagas disease; West Nile virus encephalitis

*Obtained in Denmark Sex Life Survey; UK Gay Men's Sex Survey& National Surveys of Sexual Attitudes and Lifestyles; US National HIV Behavioral Surveillance (NHBS); **ECDC core indicators

Population cohort-based surveillance

Mainly for research purposes, population cohorts and some other community-based surveillance networks have been established in several LMIC, under different formats. Many such systems can provide demographic, socio-economic, environmental, human host factors, or behavioural indicators linked to population denominators. These systems could complement facility-based case and death reporting, where such indicators lack.

Health and demographic surveillance systems (HDSS) consist of a longitudinal follow-up of a population cohort living in a well-defined geographical area, registering largely similar data such as births, migration, deaths, and exposures or health status. Data collection historically involved household visits repeated at bi-yearly intervals, but with increased phone coverage, phone calls can replace labour-intensive visits. HDSS include detailed population-denominators, as a replacement for (absent or unreliable) population registers. Observational and interventional research studies using HDSS sites have contributed to public health breakthroughs. Notable examples include the understanding that high uptake of antiretroviral therapy prevents HIV transmission, the effectiveness of cholera vaccines, as well as vaccines for *Haemophilus influenzae* type b and malaria, and established Falciparum malaria as a critical risk factor for bacteraemia (24–28). To date, in the context of infectious diseases, HDSS applications and data use have been mostly research-focused. This whilst HDSS data could resolve important limitations of facility-based disease surveillance. Repeated household surveys within the HDSS cohort can provide trends in the risk of spread of an infectious agent (e.g., changes in access to safe drinking water), the risk of infections developing in disease (e.g., the prevalence of chronic conditions), of spread between One Health compartments (e.g., keeping livestock in the house), and data on the performance of disease control programs (e.g., the uptake of bednets). If such household data is linked to health records, facility-based surveillance, serological or pathogen screening of that population, populations at risk of infection or at risk of disease progression can be identified and characterised.

HDSS household visits sometimes involve collection of specimens from members of the population cohort, searching for a specific marker or parasite in that specimen. When repeatedly collecting dried blood spot samples from the same HDSS member, seroconversions against different infectious agents and antibody levels at population level could be detected. When integrated with age-, sex- and socio-economic data of those participants, incidence and prevalence of several seasonal and

chronic infections or immunity within the population could be estimated by age, sex and subpopulation. This has been done for COVID-19 in South Africa, Mozambique, the DRC, and potentially elsewhere, but would be even more informative if continued so that long term trends in infections and its link with the loss/gain of immunity could inform e.g., catch-up vaccination campaigns, screening, etc. (29).In Maputo, Mozambique, on top of blood samples of randomly selected participants for serology, we biweekly visited households in a HDSS to collect nasal self-swabs of symptomatic cases for SARS-CoV-2 testing to determine COVID-19 incidence rate by age- and subgroup – a parameter not available in the country because testing restricted to specific admitted cases (30). HDSS could function as a network of sentinel populations, providing infection rates and correction factors to infere measures of disease occurrence from facility-based surveillance data.

Two limitations of HDSS are a potential Hawthorne effect, that data for a delimited population in one place cannot easily be extrapolated to other regions, and the high cost of maintaining such surveillance system – demanding human resources with epidemiology background (31). It is indeed possible that frequently visited households, informed about a dozen health-related issues, will respond and behave differently than they would have, had they not been in the HDSS, or than any other population in another region. Still, trends and long term changes in behaviour, exposures, or disease will still be valid, and the impact on many diseases or conditions will be minimal. It is indeed labour-intensive to continuously visit households. Moreover, in LMIC, the proportion of adults with formal employment outside home is increasing, complicating household visits during working hours. Phone calls and apps could soon replace part of the work done by interviewers, and potentially facilitate an increased frequency of follow-up. Self-reporting of behaviour and symptoms using mobile apps for the HDSS populations or for volunteers beyond a HDSS population, could allow detecting up outbreaks based on increases in syndromes reported, or could inform practices associated with disease, similar to what De Grote Griepmeting started since 2003 the Netherlands, and the ZOE COVID app recently registered in the UK (32,33).

Such participatory component in which volunteers can participate and contribute to surveillance, could also be a standalone alternative for population/community-based surveillance, potentially less resource-demanding,. The Office of National Statistics in the United Kingdom repeatedly collected nasal self-swabs by mail from randomly selected volunteers, to estimate SARS-CoV-2 infection prevalence and indicate where and when transmission was occurring in the community and anticipating increases in hospital admissions and deaths (34). Similarly, initiatives involving the public in mosquito surveillance, have recently been set up in a number of countries. interventions (35)

If timely analysed and interpreted, such estimation of risk in the population from population based surveillance can facilitate the communication of risk to general population (36). If an individual understands the risk of contracting the SARS-CoV-2 during an activity at a given point of time, from the proportion of contacts that are infected at that time, he might be more eager to change his behaviour or apply preventive measures.

Repeated health surveys

A national health survey was conducted in 1935 in the United States, as a way to obtain risk and morbidity data with reliable population denominators (37). Since the 1980s and 90s, repeated health surveys have been established in numerous LMIC under different formats. The Demographic and Health Surveys (DHS) and the Multiple Indicator Cluster Surveys are examples of widely employed household surveys. These surveys aim to monitor trends in the general population's or patients' demographic and health-related indicators and evaluate health or disease control programs.

However, use of generated data from these surveys by public health institutions, officials, and scholars from LMIC and beyond is limited or delayed for years after data collection (38). Repeated household surveys might not be best suited to reliably record case numbers. Nonetheless, other (indirect) indicators for risk, exposures, or infectious disease or AMR control can be monitored. For example hand-washing practices (WASH), vaccination coverage, insecticide-treated bednet use, disease status, or healthcare utilisation.

For AMR surveillance, repeated patient surveys or hospital-based point-prevalence surveys can provide important and low-cost surveillance on respectively community-level antibiotic use, or on hospital-level AMR, antibiotic use and infection prevention and control. In countries where the production and import of medicines is traced, sales data or records of the amount of active ingredient consumed can be used to estimate nationwide medicine and particularly antibiotic use, as illustrated by several recent papers (Hsia et al. 2019; Klein et al. 2020). If such data are absent, community-wide antibiotic use, from any formal and informal healthcare provider or from self-medication, can be obtained by weighing the quantity or prevalence of antibiotic use per provider with the frequency of health care seeking from that provider, as demonstrated in Chapter 8. Healthcare utilisation data from existing DHS and other surveys could be integrated and made accessible for this purpose. Several indicators based on the Access, Watch, Reserve-classification of antibiotics, such as the quantity or prevalence of Watch group antibiotics used and the ratio of Access to Watch antibiotics, best approximate the risk of clinically important antibiotics becoming ineffective by AMR and can guide interventions to optimize antibiotic use (19,40). A limitation of antibiotic use patient surveys is that extent of appropriateness of antibiotic use, which would require a reporting of clinical presentations and (presumptive) diagnosis, cannot be reliably determined. Also countries with advanced AMR surveillance systems, such as the Netherlands and the United Kingdom, struggle extrapolating survey findings to country-wide estimates (41). Outpatient quality of care and appropriate antibiotic use can be measured from simulated patient visits, by an actor seeking ambulatory care for a well-defined clinical picture (42). Repeated simulated patient visits have been used to evaluate antibiotic stewardship programs, e.g. at community-level in India (43).

Repeated surveys or outbreak control interventions can also provide behaviour data, such as a trend in number of contacts in the general population, which can inform infectious disease models to estimate transmission or evaluate control measures. In chapter 5 we estimated the trend in contacts reported by COVID-19 cases from contact tracing data, allowing an estimation of growth of the COVID-19 outbreak and an evaluation of physical distancing measures in place. This trend correlated well with that from a survey measuring contacts in the general population, during the same time period (44), validating contact tracing data as a proxy for contact behaviour. Sexual behaviour is repeatedly surveyed among the general population of Denmark, using the population register as a sampling frame, guiding prevention campaigns of sexually transmissible infections and HIV (45).

Sentinel primary care networks

Facility-based surveillance systems have historically been built with as primary objective reporting notifiable diseases, in order to detect outbreaks of epidemic-prone disease in different places in the country. Syndromic reporting of some seasonal infections, such as gastro-enteritis and malaria, has been integrated in facility-based case reporting surveillance systems, which is labour-intensive and does not necessarily generate accurate data. For respiratory and chronic infections, such systems are not ideal, as syndromes are not specific and different circulating infectious agents creates a high level of background noise when trying to track one. Reinforced reporting systems in sentinel primary care practices, including laboratory confirmation of a random sample of cases, could provide

information to guide influenza, COVID-19, pneumococcal, typhoid or rotavirus vaccination and future vaccination against respiratory syncytial virus and invasive non-Typhi Salmonella infections. Nevertheless, such surveillance system is labour intensive, requires great coordination between primary care practitioners, labs and public health institutes, and will only work when the generated data can effectively inform and guide vaccination programs.

I'm not aware of any such sentinel surveillance system in a low-resource setting, possibly because of its cost and because epidemiologists are scarce and already dedicated to facility-based surveillance or outbreaks of notifiable diseases. As populations are increasing mobile, ageing, and potentially vaccine hesitant, reacting to a surge of specific vaccine-preventable infectious agents may become increasing important, and require a surveillance system fit for it. By partially integrating sentinel primary care surveillance and HDSS or other population-based surveillance system, laboratory confirmed infections could be linked to demographics, exposures, underlying illness, and potentially self-reported symptoms, so that local measures of disease occurrence could be estimated and communicated.

Electronic medical records

District Health Information Software (DHIS) is an open source health information management system that allows both reporting cases of disease and recording patient's clinical and diagnostic information longitudinally in medical records in a cloud based database, which allows analysis and reporting as aggregated data. The constant generation of these data can function as a surveillance system with real-time reporting. It is particularly used in LMIC where data systems have more recently been introduced than in most industrialised countries, which often still struggle with harmonising and bringing together data originated from differing systems (46). Thanks to DHIS, several LMIC have better and harmonised electronic medical records, offering opportunities for disease surveillance without additional work load and resources needed. DHIS2 data have been used to inform the effect of free health care provision on healthcare utilisation during an Ebola outbreak in DR Congo, malaria control interventions in Burundi, for COVID-19 and measles surveillance in the DR Congo, facility-based case reports in Guinea, among several other examples (17,47–49).

When disease surveillance is combined with vaccination coverage data, control interventions can be most effectively targeted. In most LMIC, vaccination coverage is estimated by geographical area, from the number of distributed vaccines, divided by the estimated birth cohort that is supposed to be vaccinated in that area. These numbers require accurate population and fertility data and data on what proportion of distributed vaccines is actually administered – often not available (49). Electronic medical records and health information systems as DHS-2 could allow linkage between vaccination status and demographic, socio-economic, ethnic factors or health conditions, identifying specific groups at risk of outbreaks, and estimating subgroup- and age-specific vaccination coverage.

Mobility

Mobility data can be used to quantify risk that is related to mobility, such as cross-border transmission of pathogens, or as a proxy for human behaviour. During the 2013-16 West African Ebola outbreak, data on mobility of the population have been used in models demonstrating the ability to predict countries' risk of importing cases of Ebola Virus Disease, though only retrospectively – to evaluate the effect or travel restrictions, yet too late to inform policy at the time (50). Already a few years later, during the COVID-19 pandemic, such analyses were published early in the outbreak, when early travel restrictions would have been most effective, SARS-CoV-2 introductions in different countries could be predicted from flight bookings from Wuhan to different destinations globally (51,52). Mobile phone location data was used to identify activities and subgroups where COVID-19 transmission was most intense, and where control measures could be

focused on (53,54). From check-ins on social media, the relative visit frequency between different locations in Wuhan at risk for SARS-CoV-2 superspreading events could be compared, the Huanan Seafood Market turned out to be one of the least frequented locations while many early cases had a link to it, supporting evidence that the Huanan market was likely the epicentre of the SARS-CoV-2 pandemic (55).

All of the above examples were research studies. Integrating mobility data might be slower if not involving a global infectious disease threat. A validation of different sources of mobility (and behaviour or environmental) data to decide which best informs surveillance and control, would need to happen in LMIC, making data then easily accessible and linkable to disease surveillance.

One Health

The presence of vectors or animal reservoirs is sometimes searched for, yet rarely sustained at a regular interval and with a spatial distribution that allows evaluating a change in the risk of spread of infectious agents. Similarly, surveillance of animal health is usually conducted by veterinarian and in LMIC its data is not often rapidly available and interpreted by those working on human health, despite One Health compartments exchanging infectious agents and AMR genes.

Several industrialised countries use sewage surveillance systems to detect or monitor the presence of infectious agents and AMR genes from samples collected in a standardised way and without any additional workload for the healthcare system or need for people's consent. Metagenomic sequencing of sewage samples also has the potential to detect outbreaks of an infectious agent before case patients go to healthcare facilities, and to monitor the distribution of infectious agents and of AMR genes reflecting their abundance in the non-hospitalised population, not only among patients in healthcare facilities (20,56). Besides sewage, metagenomic sequencing of environmental samples, pooled vector samples, manure, or slaughterhouse waste, could help to detect infectious agents and AMR genes circulating in One Health compartments and with the potential to spill over to another (57). Currently in LMIC, metagenomic sequencing capacity for public health is largely absent, livestock is not only kept by farmers but by many households, with a majority of livestock not passing through slaughterhouses, and sewage systems are fragmented and differ between settings in terms of flow rate and populations making use of it. Nevertheless, metagenomic testing at existing laboratory hubs, as exists in Kenya, of stool, manure and environmental samples collected in a defined sampling frame of households, holds the potential to monitor trends in abundance of infectious agents and AMR genes, to infer changes in the risk of spread, or to detect new infectious agents.

Genomic surveillance

Genome sequencing, including metagenomic sequencing mentioned above, has different applications for surveillance: i) the detection in animals or in the environment of infectious agents that could pose a public health threat, ii) the detection of new infectious agents with identification of genes that could be targeted by diagnostic tools, iv) the detection of mutations or genes that could alter the characteristics of an infectious agent, such as virulence, transmissibility, resistance against antimicrobials, or escaping diagnostic tools, and v) relate cases belonging to the same outbreak, index case or source, informing outbreak investigations and control measures.

Investment in Ebola, Lassa Fever, and COVID-19 surveillance and response has increased genomic surveillance capacity in several LMIC, yet its application beyond emerging infections is limited (58). Integrating genome sequencing within public health surveillance is crucial for it to be effectively supporting the detection of outbreaks, and focusing control measures on clusters of cases.

Event-based surveillance

Large agencies as the European Centre for Disease Control and Prevention and the WHO invested major resources in event-based surveillance, which hopefully will prove its worth in coming years. Though the signals on public health threats it might generate will need well-functioning indicator-based surveillance systems to investigate signals, to tracking outbreaks once they get going, or to inform outbreak control. Countries with limited resources can probably better strengthen indicator-based surveillance systems rather than build on top of it event-based surveillance, which required specialised expertise, and can better be pooled in international agencies, such as the African CDC. Ties will need to be built between event-based surveillance expertise at international agencies and national or local surveillance and disease control teams, who can guide what and where to look for, e.g., known public health threats from historic data, and websites or social media groups to track, and investigate signals from event-based surveillance.

Outlook to future outbreak control

As the world seems now beyond the acute phase of the COVID-19 pandemic, there is renewed interest in pandemic preparedness, to prevent animal to human spillover, or to detect new outbreaks timely. We propose a number of key attributes of surveillance systems to consider when strengthening or reorienting systems. These attributes can apply to a different degree to different settings, high- or low-resource, but their relevance is demonstrated with examples from several sub-Saharan African low-income countries.

Surveillance of risk complementing facility-based case and death counts

Surveillance that detects changes in risk, rather than changes in disease, could support preventing outbreaks or reacting in an early stage of the outbreak: behaviour, environmental exposures, animal presence or animal health, population host factors, characteristics of infectious agents, or the uptake of control interventions. Delays and underreporting in disease reporting can be avoided and workload for healthcare workers decreased. Risk surveillance data will need to be accessible, integrated, regularly analysed, reported, and translated to interventions.

Real-time data availability with rapid analyses and interpretation

Rapid availability of (digital) surveillance data, their analysis and interpretation facilitates the introduction and adaptation of control measures to changing transmission dynamics, and shifts in geographical areas, or subpopulations affected. Estimating the effectiveness of control measures can be done using timely available data on both the roll-out or uptake of control measures and on (risk for) disease. A perfect illustration is again the above mentioned example of how regularly interpreted and shared sewage polio surveillance data was combined with vaccination coverage data to target catchup polio vaccination in the United Kingdom, even before a first case of paralysis was picked up (59). Other recent examples were the continued evaluation of the effectiveness of COVID-19 vaccines and global monitoring of COVID-19 variants, informing (booster) vaccination strategies as soon as the interpreted data were released (60,61)

Even if data sharing was problematic at the start of the COVID-19 pandemic, the past few years have been revolutionary in terms of rapidly sharing epidemiological, genomic and clinical raw and interpreted data, through repositories, reports, and preprint servers. Researchers could complement the work done by public health institutes, guiding and evaluating physical distancing measures. Journalists could rapidly communicate consequences of epidemiological data or research for local contexts, which helped sensitizing healthcare workers and the general public on the risk for infection and for severe disease and the effectiveness of preventive measures, facilitating targeted interventions to groups or areas most at risk.

When having to deal with different disease outbreaks at the same time, meanwhile monitoring other signals and threats can be challenging. Bringing facility-based disease surveillance and data on the risk for outbreaks and infectious agent characteristics (AMR, genomics) from laboratories together in a data cleaning and analysis pipeline, standardising and to some extent automatising signal detection, risk and threat monitoring, such as an epizootic outbreak or the emergence of a clinically relevant new AMR profile or gene, could inform preventive measures without overburdening the epidemiological human resource capacity. The experience analysing signals will allow establishing outbreak and risk indicators with thresholds at which action is required, speeding up outbreak and AMR control interventions. The thresholds applied will need to be reassessed and adapted to ensure control interventions are needed and proportional.

Dynamic case definitions

With data shared and analysed in real-time, case definitions could be adapted to changing likelihoods of being a case throughout an outbreak or likelihoods of an infection having a specific AMR profile, by integrating the latest epidemiological and infectious agent characteristics in the case definition. Data to inform this dynamic case definition may include the latest geographical distribution of cases, occupational risks, specific setting-related clusters, AMR profiles from susceptibility testing or genomic data of the underlying pathogen. To diagnose or rule out Ebola, static case definitions and clinical predictions scores performed suboptimal (62–65), as also illustrated in chapter 2. A dynamic case definition including geographical proximity to recent clusters of cases, of which changes throughout the outbreak are taken into account, could improve diagnostic performance and timeliness, and as a result decrease barriers for potential cases to seek testing.

Again access to technology, here an electronic and connected assessment form at health facility admission, is required for a case definition taking several changing criteria into account. Currently case definitions are kept as simple as possible, to guarantee harmonised application by different healthcare workers. Having such dynamic assessment would make it also easier to use clinical prediction scores. Scores are often developed but too complex to apply in a low-resource healthcare facility where healthcare workers are already overstretched and with few infectious disease physicians.

Better integration of laboratory data

If diagnostic tests are lacking, it often still is useful to monitor clinical disease occurrence, provided healthcare utilisation is stable. Yet for clinical disease without differentiating symptoms, such as persistent fever, watery diarrhoea, or lower respiratory tract infection, it might take a while before a clear increase in cases, above a baseline level of similar syndromic cases, can be distinguished. With diagnostic tests, most of the baseline syndromic cases can be excluded, and outbreaks more easily and rapidly detected. During foodborne outbreaks in industrialised countries, it used to be difficult to distinguish outbreak cases from sporadic cases, which occur throughout the year and in all regions. With the introduction of genome sequencing of the identified food-borne pathogens, distinct clusters of cases originating from the same source can be differentiated from other outbreaks and endemic or sporadic cases (66), improving specificity and timeliness of outbreak detection. This in turn facilitates investigating only outbreak cases, so that finding a common outbreak source is easier and targeted interventions can rapidly be introduced to stop the outbreak. Even if sequencing specimens from any case of disease is not feasible or affordable, examples as lateral flow testing for malaria and COVID-19 and point-of-care molecular testing for tuberculosis, described earlier, demonstrate further progress on point-of-care diagnostics is possible in LMIC.

Considering their cost for the patient, tests will usually only be done if relevant for clinical decisions benefitting the patient's health. The relevance for surveillance will not always be considered. Public

funding could contribute to increasing testing capacity which benefits infectious disease surveillance.

For surveillance and disease control purposes, it is important that results of diagnostic testing are accessible available in real-time, and linkable to clinical case or death reporting. Reporting standards and databases should be harmonised, deciding on unique identifiers to link clinical, laboratory and demographic data (67). How outbreak control can benefit from rapid access and linkage of test results, has been well demonstrated by COVID-19 contact tracing apps. Testing results were linked to the automatically recorded contacts someone with COVID-19 had in days prior to the positive test, notifying high-risk contacts. Apps identified more contacts than over-the-phone contact tracing, which were as likely to be infected than contacts reported over the phone and the app was faster to notify contacts, resulting in faster quarantine of contacts (68). Despite successful use of such apps in few countries, engaging sustained uptake and use of the app by communities requires evaluating and communicating the apps' effectiveness to the public, though this has not been done in most countries (69). These apps could also make their users aware of potential exposure to SARS-CoV-2, engaging them to prevent transmission.

Population denominators

When population or health registers are absent, no denominators are available to estimate measures of disease frequency from facility-based reported case numbers, even though it could help set priorities between disease control interventions. Establishing such registers will require time and resources. Meanwhile, a few options could help estimate disease occurrence with a population denominator. For diseases without strong spatial heterogeneity, the incidence of disease diagnosed in facilities could be estimated within a HDSS cohort. When correcting with the proportion of HDSS participants who seek care at those facilities for such clinical presentation, the disease incidence in the HDSS population can be estimated. Inferring to the general population can then be done by weighing age/sex/other-factor-specific incidence for their distribution in the general population. For diseases without spatial heterogeneity, population denominators corresponding to case numbers in facilities could be estimated from an indicator condition with universal or well understood healthcare use, such as facility-based deliveries. Using the fertility rate, the number of deliveries may be extrapolated to a number of women of childbearing age, from which the population covered by that facility could be estimated. Again, correcting for healthcare utilisation might be needed, where survey data might come in handy. Data on the number of deliveries, of diagnoses of a disease, and more, are increasingly available in countries with harmonised electronic medical records, as discussed earlier.

Even though linking health and population data might be challenging in most countries, linking death registers to census data has proven to be feasible in numerous LMIC, providing valuable data to inform disease control. Currently, South Africa is the only country on the sub-Saharan African mainland that has a robust civil birth and death registry, which has accessible data and has proven its value estimating the true burden of the COVID-19 pandemic. The Africa Centres for Disease Control and Prevention African CDC started a Mortality Surveillance Program to deduct birth and cause-specific mortality rates from verbal autopsies of all deaths within a representative sample of a few percentages of the total population (70). Excess mortality surveillance compares the mortality rate with the rate expected that time of the year, based on historic data. Compared to a mortality rate based on facility-based death counts, excess mortality is not affected by misdiagnoses of underlying death causes and underreporting of deaths (71). Verbal autopsies help to associate a cause of death to each death, so that age- and cause-specific mortality can be estimated.

Better targeting of risk groups

Currently in most settings, facility-based notifiable disease reports are aggregated, and even if often collected, demographics, socio-economics, exposures, underlying conditions or risk behaviour are not readily reported and communicated to healthcare workers and the public – sometimes rightly so for confidentiality. Better linkage of risk, disease, and population data will eventually result in a better identification of groups at increased risk of (an AMR) infection, of infecting others, of disease, of hospitalisation and of death. Targeted interventions, differentiating between risk profiles, is efficient and has been very successful in most disease control programs. Linkage between surveillance outcomes and demographic, health, behavioural, environmental and other risk factors should be facilitated in real time to guide interventions, and be limited to research completed months after the outbreaks are over.

Conclusion

For infectious disease surveillance to fully live up to its potential to inform and target disease control, it needs to go beyond facility-based case reporting, exploit data on factors affecting the risk of outbreaks and of rising AMR, and analyse and interpret such data, preferably even before an acute outbreak needs all attention and disrupts routine care. In LMIC, surveys and population cohorts could be used to supplement national surveillance systems to provide population denominators, demographics, exposure and risk factor data - mostly lacking now.

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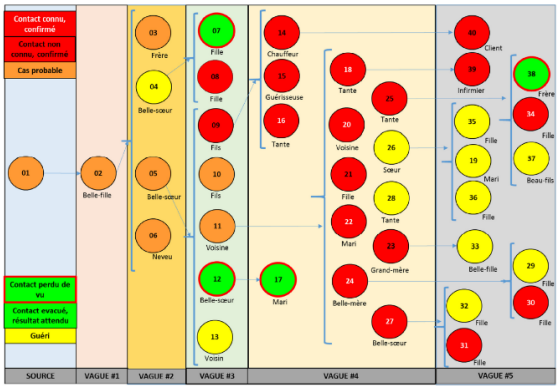
10- Samenvatting

Dit proefschrift heeft tot doel een kritische beoordeling te geven van de rol van ziektesurveillance bij de preventie en bestrijding van infecties, zowel bij uitbraken als daarbuiten, en voorstellen te doen voor veranderingen in de bestaande surveillance of voor alternatieve gegevensbronnen, die sneller bedreigingen kunnen detecteren en bestrijdingsmaatregelen informeren of evalueren.

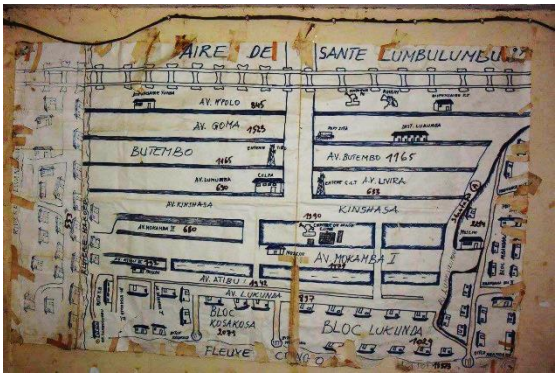


Ebola Virus Disease transmission chain, Forécariah préfecture, Guinea, August 2015. Investigation team MSF, OMS, UA, CDC

Doeltreffende maatregelen ter bestrijding van een uitbraak vereisen een **tijdige en nauwkeurige identificatie van de ziektegevallen**. De belangrijkste bestrijdingsmaatregel tijdens de Ebola uitbraak in West-Afrika in 2014-2016 (hoofdstuk 2) was de isolatie van bevestigde gevallen. Patiënten met een combinatie van symptomen, al dan niet gelinkt aan een bevestigd Ebola geval, werden opgenomen in isolatie- en behandelingscentra. Daar werden ze aan één (of meerdere indien minder dan 72 uur na het begin van de symptomen) PCR-test(s) onderworpen, ter bevestiging van een infectie met Ebolavirus.

Testen nam dagen in beslag vanwege niet frequent afnemen van bloedstalen, transport van de stalen, de doorlooptijd in een gecentraliseerd laboratorium, en het rapporteren van de resultaten. Die gedwongen opname tijdens het testen vormde voor patiënten met koorts een belemmering om zich te laten testen, en zo – indien besmet met Ebolavirus – zich tijdig te isoleren. Het vertraagde ook de doorverwijzing van niet-Ebola-gevallen, waarvan sommige ernstig ziek waren, waardoor aangepaste zorg vertraging opliep. Bovendien bleek de gevaldefinitie die werd gebruikt om te beslissen over opname/isolatie slecht te presteren op zowel sensitiviteit (gepoold 81,5%) als specificiteit (gepoold 35,7%) (Caleo et al., Lancet Infect Dis, 2020). Een aangepaste gevaldefinitie of predictiescore, op basis van alleen klinische gronden, laten niet toe meer vermoedelijke gevallen uit te sluiten. Tijdens de uitbraak van gele koorts in de DRC in 2016 (hoofdstuk 3) werd de gevaldefinitie voor de ziektesurveillance verder gebruikt. Het doel van die gevalsdefinitie is te waarschuwen voor potentiële uitbraken zonder al te veel valse alarmen, dus maximale specificiteit: aanwezigheid van geelzucht is essentieel. Geelzucht treedt echter pas op na meer dan een week na het begin van de symptomen, waardoor vroege opsporing van gevallen en bijhorende controlemaatregelen, zoals bescherming tegen muggen, isolatie van de patiënten (weg van de vector), tracering van contacten, en muggen verdelging in de omgeving van de patiënten, vertraging oplopen. Gevalsdefinities voor ziektesurveillance zijn gewoonlijk statisch en worden niet snel aangepast aan veranderende transmissie-dynamiek of aan geografische foci. Tijdens een epidemie moeten gevalsdefinities bijgesteld kunnen worden in functie van die veranderende situaties, en een moet een evenwicht gevonden worden tussen enerzijds het opsporen van alle mogelijke gevallen, bijvoorbeeld om ze vroegtijdig te isoleren of te behandelen om de overdracht te beperken, en anderzijds het voorkomen dat

teveel mogelijke ziektegevallen moeten onderzocht worden of dat patiënten dagenlang in isolatie terechtkomen door traag testen.

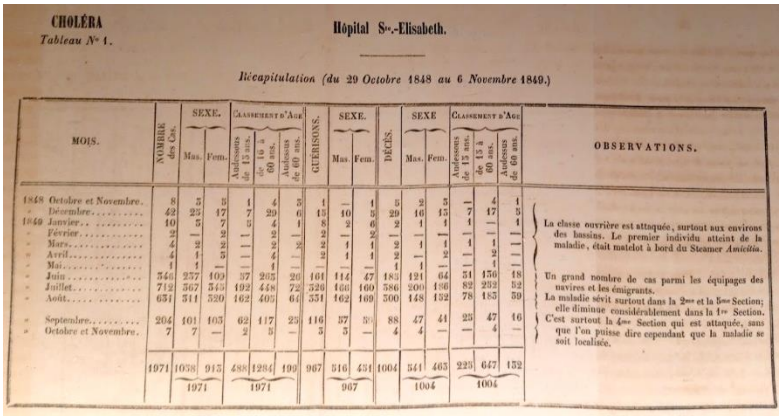


Wanneer maatregelen ter preventie of bestrijding van een uitbraak worden ingevoerd nadat een grens in het aantal gevallen, gerapporteerd in de ziektesurveillance, overschreden wordt, worden die maatregelen inherent vertraagd genomen. Afhankelijk van de ziekte is dat problematisch dan wel aanvaardbaar. Om tijdig te reageren bij uitbraken van infectieziekten met sterk groeipotentieel – cholera in niet endemisch gebied, COVID-19 – kan het **risico op een uitbraak** beter gebruikt worden om interventies op te starten, of om interventies op specifieke bevolkingsgroepen of regio's te richten. Om gebieden en bevolkingslagen te identificeerden die prioriteit moeten krijgen voor orale choleravaccinatie of investeringen in water- en sanitaire infrastructuur in DR Congo, analyseerden we de terugkerende geografische verspreiding van cholera tussen 2008 en 2017, waaruit we afleidden waar uitbraken en hoge sterfte kan worden verwacht tijdens een toekomstige epidemie (hoofdstuk 4). Ook gegevens die toelaten risicogedrag te monitoren over de tijd kunnen bestrijdingsmaatregelen tijdig informeren of het effect in te schatten van verschillende interventies op de groei van de epidemie. We konden aan de hand van de trend in het gemiddelde aantal gerapporteerde risicocontacten uit de COVID-19-contactopsporing, veranderingen in de dagelijkse COVID-19 incidentie modelleren, en inschatten welke combinatie van interventies voldoende kan zijn om de viruscirculatie laag te houden (hoofdstuk 5). Het aantal door bevestigde COVID-19 gevallen gerapporteerde contacten was niet accuraat in vergelijking met contactbevragingen specifiek uitgevoerd om contacten te meten, maar de trend in het aantal gerapporteerde contacten over de tijd uit de operationele gegevens volgde die van de contactbevragingen.

Ook bij maatregelen om antibioticaresistentie te bestrijden in laag- en middeninkomenslanden, waar bacteriën op gemeenschapsniveau resistentie verwerven of er verder verspreid worden, is klassieke ziektesurveillance soms ontoereikend, vertraagd of onbestaand. In tegenstelling tot geïndustrialiseerde landen, is toegang tot ziekenhuizen en diagnostiek beperkt en is de ziektelast van antibioticaresistentie niet hoofdzakelijk toe te schrijven aan ziekenhuisinfecties, dus speelt antibioticagebruik binnen ziekenhuizen wellicht een beperktere rol. Opvolgen van veranderbare risicofactoren, zoals antibioticagebruik of hygiënische omstandigheden op gemeenschapsniveau, of dragerschap van resistente bacteriën in de algemene bevolking, kan toelaten interventies gericht op deze risicofactoren beter te focussen en te evalueren – ook wanneer klassieke ziekenhuissurveillance, aan de hand van bacteriële bloedcultuur bij invasieve infecties, afwezig is. De surveillance van ambulant antibioticagebruik wordt echter bemoeilijkt door een belangrijk aandeel van antibioticagebruik via zelf-medicatie, voorschriftvrij verkregen. We bepaalden het aandeel van verschillende zorg- en geneesmiddelverstrekkers in de laatste hoofdstukken, met als

doel mogelijke pistes voor **antibioticagebruik surveillance op bevolkingsniveau**, grotendeels afwezig in lage-inkomenslanden, te verkennen. In een systematische review (hoofdstuk 6) hebben we eerst de omvang van **zelfmedicatie met antibiotica** in Afrikaanse landen geschat: meer dan de helft van de bevolking gaf aan de afgelopen maanden zelf antibiotica zonder voorschrift gebruikt te hebben, met grote verschillen tussen gebieden en studies. Vervolgens hebben we aan de hand van bestaande gegevens van patiëntenbevragingen bij ziekenhuisopname, het **ambulant antibioticagebruik vóór ziekenhuisopname** gekwantificeerd in Cambodja, DR Congo, Nepal en Soedan (hoofdstuk 7). Ambulant antibioticagebruik (via eerstelijnszorg of voorschriftvrij) kwam het vaakst voor in Nepal, waar bovendien de grote meerderheid Watch antibiotica betrof, cruciale antibiotica om klinisch belangrijke infecties te behandelen die bedreigd worden door antibioticaresistente. Omdat bestaande gegevens niet toe laten te analyseren waar en wanneer antibiotica werden verkregen, noch dosis en indicatie vermeldden, gingen we in hoofdstuk 8 de frequentie van ziekte en bezoeken aan zorg- en geneesmiddelverstrekkers, uit bevragingen in huishoudens, combineren met prevalentie van antibioticagebruik, uit patiëntenbevragingen na een bezoek bij elk type geneesmiddelvoorschrijver of -verstrekker. We schatten zo **antibioticagebruik per capita, via elke verstrekker** in twee districten in DR Congo. Bezoeken aan zorgverstrekkers waren beperkt, al zeker aan ziekenhuizen, wat zich vertaalt in een totaal antibioticagebruik per capita dat laag ligt in vergelijking met andere landen. Meer dan de helft van de gebruikte antibiotica, met nog een groter aandeel van Watch-antibiotica, werden verstrekt via private zorgverstrekkers zoals private apotheken of klinieken, buiten het publieke gezondheidssysteem. Interventies om antibioticaresistentie te bestrijden moeten zich ook op private of informele verstrekkers richten, wat nu nauwelijks gebeurt.

Klassieke ziektesurveillance richt zich ook vaak minder op de private zorgverstrekkers, wat resulteert in vertraagde detectie of missen van ziektegevallen. Dit sluit aan op de algemene discussie, waarin ik argumenteer dat ziektebestrijding- of ziektepreventiemaatregelen tijdens grote uitbraken niet enkel kan berusten op het tellen van ziektegevallen en sterfgevallen, wat een vertraagd of onvolledig beeld geeft. Gegevens van vroegere uitbraken of alternatieve gegevensbronnen die toelaten het **risico op epidemieën of toegenomen antibioticaresistentie te meten**, zoals programmatische gegevens, menselijke gedrag, herhaalde gezondheidsbevragingen, of prospectieve opvolging van een bevolkingscohort, kan toelaten **vroeger en gerichter preventie- of bestrijdingsmaatregelen in te zetten**.



CHOLÉRA
Tableau N° 1.

Hôpital Se.-Elisabeth.

Récapitulation (du 29 Octobre 1848 au 6 Novembre 1849.)

MOIS.	NOMBRE des Cas.	SEXE. Mas.	SEXE. Fem.	CLASSEMENT D'AGE. Audessous de 15 ans.	CLASSEMENT D'AGE. de 16 à 60 ans.	CLASSEMENT D'AGE. Audessus de 60 ans.	GUÉRISONS.	SEXE. Mas.	SEXE. Fem.	DÉCÈS.	SEXE Mas.	SEXE Fem.	CLASSEMENT D'AGE Audessous de 15 ans.	CLASSEMENT D'AGE de 16 à 60 ans.	CLASSEMENT D'AGE Audessus de 60 ans.	OBSERVATIONS.
1848 Octobre et Novembre.	8	3	5	1	4	3	1	—	1	5	3	3	—	4	1	La classe ouvrière est attaquée, surtout aux environs des bassins. Le premier individu atteint de la maladie, était matelot à bord du Steamer *Amicitia*.
» Décembre.	42	25	17	7	29	6	15	10	5	29	16	13	7	17	5	
1849 Janvier.	10	5	7	5	4	1	8	2	6	2	1	1	1	—	1	
» Février.	2	—	2	—	2	—	2	—	2	—	—	—	—	—	—	
» Mars.	4	2	2	—	2	2	2	1	1	2	1	1	1	1	—	
» Avril.	4	1	3	—	4	—	2	1	1	2	—	2	—	2	—	
» Mai.	1	—	1	—	1	—	—	—	—	1	1	—	—	1	—	
» Juin.	544	257	109	37	265	26	104	114	47	185	121	64	21	150	18	Un grand nombre de cas parmi les équipages des navires et les émigrants. La maladie sévit surtout dans la 2me et la 3me Section; elle diminue considérablement dans la 1re Section. C'est surtout la 4me Section qui est attaquée, sans que l'on puisse dire cependant que la maladie se soit localisée.
» Juillet.	712	367	345	102	448	72	326	166	160	386	201	186	82	252	52	
» Août.	651	311	320	162	405	64	331	162	169	300	148	152	78	185	59	
» Septembre.	204	101	103	62	117	25	116	57	59	88	47	41	25	47	16	
» Octobre et Novembre.	7	7	—	2	5	—	5	5	—	4	4	—	—	4	—	
	1971	1038	915	488	1284	199	967	516	451	1004	541	463	225	647	132	
		1971		1971			967			1004			1004			

Report of hospital admissions during the 1849 cholera outbreak in Antwerp, Property Stadsarchief Antwerpen.

11- Acknowledgements

I have been hesitant to combine the previous chapters in a PhD thesis, considering how outbreaks, contexts, settings and diseases diverged. Marianne has been insisting though that waiting for everything to converge could take time or may never happen. In 2023, we can assume policy makers are to a certain degree aware of the need to detect outbreaks timely, to respond timely and on an appropriate scale o the appropriate extent, and to evaluate outbreak control measures – all while engaging policymakers and communities. Perhaps it is not bad timing to highlight some shortcomings of existing surveillance systems and control measures, and propose some solutions or different approaches.

I'm particularly grateful to the people who taught me how to interpret infectious disease (outbreak) data and how to best write that down: Marianne van der Sande, who combined granting lots of freedom with really supportive and constructive feedback. My co-supervisor Esther van Kleef, who's an AMR and stats library, lifting some papers and analyses to a next level, and who's always in for a scientific brainstorm. Henriette de Valk, Kostas Danis and Christian Winter for the intensive feedback during my EPIET fellowship, sharing their experience to build field epi skills. Tom Decroo and Anja de Weggheleire for relentless patience throughout dozens of makeovers of my first paper – chapter 2 in this thesis. Jan Jacobs for introducing me into the world of AMR and microbiology, and insisting on fair and robust data interpretations. Daniel Valia, Eugene Yeika, Andrea Nebbioso, and Victor Dara, whom I was privileged to support in MPH thesis writing. They provided me great insight in infectious disease issues in their home countries. We continue working together in what is now a multi-country community AMR network, and set up a first community AMR intervention cluster RCT. Liselotte Hardy, Anne-Sophie Heroes, Barbara Barbé and Bieke Tack from Jan Jacobs' research group relentlessly support a bacterial bloodstream infection surveillance network in low- and middle-income countries, allowing me to hitch our community AMR wagon to. Placide Mbala, Octavie Lunguya (and team), and Delphin Phanzu, for their interest in putting AMR to the forefront in the DR Congo. Marc Bonten for PhD supervision, but also for his blogposts – eye opening in what's known and not known when it comes to AMR in Europe. Many collaborators set up and conduct field studies, often logistically complex and tiring, yet display relentless enthusiasm to get a study done: Bijou Mbangi, Mi Budiongo, Sidibou Yougbaré, Ferrão Mandlate, Nilzio Cavele and many more. Finally, writing papers started out as a hobby project, in between field work with MSF and Epicentre, and Eveline had to endure I spent many evenings in from of computer screens, and yet she never left me, for which I am infinitely grateful.

12- About the author

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Invited lectures: “The interplay between community-level antibiotic use and AMR transmission in sub-Saharan Africa and implications for stewardship intervention bundles”, ESCMID Education Course Antimicrobial Stewardship in Low- and Middle-income countries, 2023; “Réduire le risque d’infection résistante aux antimicrobiens au niveau communautaire”, Conférence Scientifique, Université Kasa-Vubu, Boma, DR Congo, 2022; “Infectious Disease Epidemiology” PhD course Université Catholique de Louvain, Belgium, 2019; “Cholera epidemiology in DR Congo 2008-17” ITM Lecture, ITG, Belgium 2017.

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