

**Access to and use of medicines among Syrian asylum seekers and refugees in
Germany and the population with government health insurance in Syria**

Dissertation

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To all refugees

Abstract

Access to medicines is a critical element of health systems. The importance of medicines in promoting health and curing diseases makes access to medicines a key indicator of a country's progress towards universal health coverage (UHC). Drug utilization research is a common method for studying access to medicines. Populations affected by humanitarian crisis experience unique challenges in accessing medicines. Drug utilization among these population is understudied. Therefore, the overall aim of this thesis is to describe drug utilization among two populations: asylum seekers and refugees in Germany, and the population with government health insurance in Syria.

This cumulative thesis included four studies. Studies I and II are based on primary patient-reported data collected via a structured questionnaire from 1,641 Syrian asylum seekers and refugees in North Rhine-Westphalia (NRW), Germany, and analyzed barriers limiting access to medicines, the diagnoses that led to using the medicines as well as the patterns and rates of medicines used. Language barriers had the strongest effect on accessing medicines among participants. This was followed by barriers related to purchasing a medicine without a prescription. We observed a stronger effect of language barriers in females, those older than 50 years of age, those with chronic illnesses. In regard to the diagnoses that led to using medicines, four of the ten most commonly reported reasons for medicine use among adult asylum seekers and refugees were chronic conditions: hypertension, diabetes, stroke prevention, and hypothyroidism.

Studies III and IV were based on secondary data acquired from health insurance providers that recorded prescribed medicines dispensed for 81,314 beneficiaries over a 12-month period as outpatient care in regions controlled by the Syrian government. Through these data, we examined the rates and patterns of dispensing outpatient antibiotic, cardiovascular diseases (CVD), and diabetic medicines, and explored age, sex, and regional variation in the dispensing of these medicines. Outpatient antibiotic dispensing was mainly expressed as the number of defined daily doses (DDDs) per 1000 people per day (DID). We observed high rates (20.1 DID) of outpatient antibiotic dispensing. This included high rates of broad-spectrum antibiotic dispensing. Of the AWaRe classification, the Watch group had the biggest percentage of OAD (13.26 DID), followed by the Access and the Reserve groups (6.55 and 0.17 DID, respectively). These results are concerning as the excessive consumption of broad-spectrum antibiotics may

significantly increase antibiotic resistance. CVDs and diabetes medicine dispensing rates (306.1 DIDs, 35.7 DIDs respectively) were low during the study period and included very low rates of insulin dispensing (1.0 DID). The rates of CVDs and diabetes medicines dispensing were lower among female beneficiaries (249.6 DIDs) compared to males (388.8 DIDs). There was also significant regional variation, with low CVDs and diabetes medicines dispensing rates and very low to no insulin dispensing in some governorates that the Syrian government partly controlled.

In conclusion, we recommend applying more effort to enhancing the ability of asylum seekers and refugees to learn the German language as a mid- to long-term strategy to overcome language barriers. Particular focus should be placed on female refugees, older refugees, and those with chronic diseases or disabilities. We also recommend providing translated medical leaflets for patients who ask for them. The high prevalence of medicine use for non-communicable diseases (NCDs) medicines we observed among Syrian asylum seekers and refugees in Germany raises the question of whether enough attention has been paid to developing policies and clinical practices to ensure NCDs care in the asylum seekers and refugees' populations in Germany. This outcome also indicates a need to rethink the healthcare policies for these populations. The high rates of outpatient antibiotic dispensing among the population with government health insurance in Syria and high rates of broad-spectrum antibiotic dispensing are concerning as the excessive consumption of broad-spectrum antibiotics may significantly increase antibiotic resistance. On the other hand, the low rates of NCDs medicines dispensing among the population with government health insurance in Syria suggest that these diseases are undertreated in a country affected by conflict, such as Syria. We encourage future studies to pay more attention to the detection, treatment, and management of NCDs among forcibly displaced populations and populations living in conflict zones and consider cultural issues that might influence access to medicines. More efforts are needed to investigate the quality, availability and affordability of medicines in different settings and among different groups of Syria's population, especially in the regions that are not under the Syrian government's control.

Zusammenfassung

Der Zugang zu Arzneimitteln ist ein wichtiges Element der Gesundheitssysteme. Die Bedeutung von Arzneimitteln für die Gesundheitsförderung und die Behandlung von Krankheiten macht den Zugang zu Arzneimitteln zu einem Schlüsselindikator für die Fortschritte eines Landes auf dem Weg zu einer universellen Gesundheitsversorgung (UHC). Die Arzneimittelanwendungsforschung bietet wichtige Methoden für die Untersuchung des Zugangs zu Arzneimitteln. Bevölkerungsgruppen, die von humanitären Krisen betroffen sind, erfahren häufig verschiedene Herausforderungen beim Zugang zu Arzneimitteln. Die Arzneimittelanwendung in diesen Bevölkerungsgruppen ist bis dato wenig erforscht. Diese Doktorarbeit untersucht den Arzneimittelgebrauch bei zwei Bevölkerungsgruppen: bei syrischen Geflüchteten in Deutschland und innerhalb der Bevölkerung mit gesetzlicher Krankenversicherung in Syrien.

Diese kumulative Dissertation umfasst vier Studien. Die Studien I und II basieren auf Primärdaten, die über einen strukturierten Fragebogen erhoben wurden. Dieser Fragebogen wurde von 1641 syrische Geflüchteten in Nordrhein-Westfalen beantwortet. Analysiert wurden Daten zu Barrieren, die den Zugang zu Arzneimitteln bei syrischen Geflüchteten in Deutschland einschränken. Analysiert wurden auch Daten zum Arzneimittelverbrauch und den Diagnosen, die zur Anwendung dieser Arzneimittel geführt haben. Sprachbarrieren hatten den stärksten Einfluss auf den Zugang zu Arzneimitteln. An zweiter Stelle folgten Barrieren im Zusammenhang mit dem Kauf von Arzneimitteln ohne Rezept. Es konnte ein größerer Einfluss der Sprachbarrieren bei weiblichen Teilnehmerinnen, bei Teilnehmer*innen, die älter als 50 Jahre sind, sowie bei Teilnehmer*innen mit chronischen Erkrankungen festgestellt werden. Die Gründe, die zur Anwendung dieser Arzneimittel geführt haben, waren vier der zehn am häufigsten chronischen Erkrankungen: Hypertonie, Diabetes, Schlaganfall und Hypothyreose.

Die Studien III und IV basieren auf Daten von gesetzlichen Krankenkassen, die verschriebene Medikamente zur ambulanten Versorgung der Bevölkerung in Syrien erfassen. Anhand dieser Daten wurde die ambulante Abgabe von Antibiotika, von Herz-Kreislauf-Erkrankungen Medikamenten und von diabetischen Arzneimitteln untersucht. Zusätzlich wurde das Alter, das Geschlecht und regionale Unterschiede bei der Abgabe dieser Arzneimittel berücksichtigt. Es wurde eine hohe Abgabe von Antibiotika (20.1 DIDs) festgestellt, insbesondere auch von Breitbandantibiotika. Im Hinblick der AWaRe-Klassifizierungssystem hatte die Watch-Gruppe

den größten Anteil der abgegebenen Antibiotika (13,26 DIDs), gefolgt von der Access- und der Reserve-Gruppe (6,55 DIDs und 0,17 DIDs). Diese Ergebnisse sind besorgniserregend, da der übermäßige Konsum von Breitbandantibiotika die Antibiotikaresistenz signifikant erhöhen kann. Die Abgaberraten von Herz-Kreislauf-Medikamenten und diabetischen Arzneimitteln (306.1 DIDs und 35.7 DIDs) waren während des Studienzeitraums niedrig und beinhalteten sehr geringe Abgaberraten von Insulin (1.0 DID). Diese Abgaberraten waren niedriger bei weiblichen Probanden (249.6 DIDs) als bei männlichen Probanden (388.8 DIDs). Erhebliche regionale Unterschiede konnten in einigen Gebieten, die teilweise von der syrischen Regierung kontrolliert wurden, im Hinblick auf niedrige Abgaberraten von Herz-Kreislauf-Medikamenten und diabetische Arzneimittel erfasst werden. Das schließt in bestimmten Regionen von Syrien niedrige bis gar keiner Abgabe von Insulin ein.

Zusammenfassend lautet die Empfehlung aufgrund der Ergebnisse, die Sprachkompetenz bei Geflüchteten als mittel- und langfristige Strategie zu fördern, um den Zugang zu Arzneimitteln zu optimieren. Besondere Aufmerksamkeit sollte auf die folgenden Subgruppen der Geflüchteten gelegt werden: Frauen, ältere Menschen sowie Geflüchtete mit chronischen Krankheiten oder Behinderungen. Auch sollten Patient*innen, übersetzte Packungsbeilage zur Verfügung gestellt werden. Die hohe Prävalenz der Arzneimittelanwendung bei nichtübertragbaren Krankheiten, die bei syrischen Geflüchteten in Deutschland beobachtet wurde, wirft die Frage über die Angemessenheit der ergriffenen Maßnahmen zur medizinischen Versorgung von Geflüchteten in Deutschland auf. Die hohen Abgaberraten von Breitbandantibiotika in der Bevölkerung mit gesetzlicher Krankenversicherung in Syrien sind besorgniserregend, da ein solcher Konsum von Breitbandantibiotika die Antibiotikaresistenz deutlich erhöhen kann. Zugleich deuten die niedrigen Abgaberraten von Arzneimitteln bei nichtübertragbaren Krankheiten darauf hin, dass diese Krankheiten in der Bevölkerung in Syrien unterbehandelt sind. Es ist wünschenswert, dass zukünftige Studien zur Gesundheitsversorgung im einschlägigen Bereich mehr Aufmerksamkeit auf die Prävention und die Behandlung von nichtübertragbaren Krankheiten legen. Diese Studien sollten idealerweise kulturelle Aspekte, welche die Arzneimittelanwendung wesentlich beeinflussen, einbeziehen. Es sind weitere Studien erforderlich, um die Qualität, Verfügbarkeit, und Bezahlbarkeit von Arzneimitteln in verschiedenen Regionen und bei verschiedenen Bevölkerungsgruppen Syriens zu untersuchen.

List of scientific articles

This cumulative thesis is based on the following original articles, referred to in the text by their Roman numerals:

- I. **Aljadeeah S**, Wirtz VJ, Nagel E. Barriers to accessing medicines among Syrian asylum seekers and refugees in a German federal state. *Int J Environ Res Public Health* 2021;18(2). doi:10.3390/ijerph18020519.
- II. **Aljadeeah S**, Wirtz VJ, Nagel E. Cross-sectional survey to describe medicine use among Syrian asylum seekers and refugees in a German federal state: looking beyond infectious diseases. *BMJ Open* 2021;11(9):e053044. doi:10.1136/bmjopen-2021-053044.
- III. **Aljadeeah S**, Wirtz VJ, Nagel E. Outpatient antibiotic dispensing for the population with government health Insurance in Syria in 2018-2019. *Antibiotics* (Basel) 2020;9(9). doi:10.3390/antibiotics9090570.
- IV. **Aljadeeah S**, Nagel E, Wirtz VJ. Outpatient cardiovascular diseases and diabetes medicines dispensing in the population with government health insurance in Syria between 2018 and 2019: a retrospective analysis. *BMC Health Serv Res* 2021;21(1):1088. doi:10.1186/s12913-021-07124-6.

Scientific papers not included in this thesis:

1. **Aljadeeah S**. Are Refugees (Really) a Hard-to-Survey Group? : Fieldwork Experience with Syrian Refugees in Germany. *Journal of Refugee Studies*. 2022;feac025, <https://doi.org/10.1093/jrs/feac025>.
2. James R, Osborne R, **Aljadeeah S**, Hosseinalipour S, Traianou A, Patel S, Tatsi C, Szocs E. If global health equity is to stand a chance, the UK must cancel its plans to offshore asylum seekers to Rwanda. *BMJ Global Health Blog*. 2022: <https://blogs.bmj.com/bmjgh/2022/05/08/if-global-health-equity-is-to-stand-a-chance-the-uk-must-cancel-its-plans-to-offshore-asylum-seekers-to-rwanda/>.
3. Tomas A, **Aljadeeah S**. The Overlooked Issue of Outpatient Combination Antibiotic Prescribing in Low- and Middle-Income Countries: An Example from Syria. *Antibiotics* 2022; 11(1):74. <https://doi.org/10.3390/antibiotics11010074>.

List of abbreviations

AsylbLG: Asylum Seekers Benefit Act

ATC: Anatomical Therapeutic Chemical Classification

CVD: Cardiovascular Disease

DDD: Defined Daily Dose

DDED: Number of Defined Daily Doses per 1000 Medicine Dispensing Events per Day

DEGS: German Health Interview and Examination Survey for Adults

DID: Defined Daily Dose per 1000 Beneficiaries per Day

EHIC: Electronic Health Insurance Card

KiGGS: German Health Interview and Examination Survey for Children and Adolescents

LMICs: Low- and Middle-Income Countries

NCD: Non-Communicable Disease

NRW: North Rhine-Westphalia

OTC: Over-The-Counter

RSAC: Refugee Shared Accommodation Center.

SDGs: United Nations' Sustainable Development Goals

UHC: Universal Health Coverage

UNHCR: United Nations High Commissioner for Refugees

WHO: World Health Organization

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1. Preface

Before joining the University of Bayreuth and starting my PhD, I worked in the humanitarian healthcare sector with forcibly displaced populations in Syria and Germany. During the course of my work in both countries, I observed the challenges associated with accessing healthcare services faced by populations affected by conflict. As a pharmacist, I had a special interest in the access to and use of medicines among these populations. Given my experience and knowledge concerning access to healthcare for asylum seekers and refugees in Germany, my skills were requested for a research project on the morbidity of asylum seekers in Bavaria conducted at the University of Bayreuth and financed by the Bavarian State Ministry of Health and Care. While there, I became interested in research methods that could help provide information that would lead to better access to and use of healthcare services among forcibly displaced populations. This led me to the idea of planning and initiating my PhD work.

This thesis is based on drug utilization research among two populations: Syrian asylum seekers and refugees in the state of NRW, Germany, and the population in Syria with government health insurance. Both groups face various challenges in accessing medicines. Moreover, the use of medicines in both populations is underreported in the literature. Therefore, in this thesis, I used two different data sources to describe the patterns and rates of medicine use and addressed the challenges in accessing medicines facing both populations.

2. Introduction

The use of medicines is the most common intervention in healthcare and constitutes an essential part of disease prevention, treatment and management [1]; thus, access to medicines is a critical element of health systems [2, 3]. This is particularly important as medicines account for the second largest component (after salaries) of most health systems in high-income countries and is the largest component of private health expenditure in low- and middle-income countries (LMICs) [4]. A well-functioning health system ensures equitable access to quality-assured medicines at a costs that the community and the households can afford [5]. Furthermore, the importance of medicines in promoting health and curing diseases makes access to medicines a key indicator of a country's progress towards UHC [2]. Drug utilization research is a common method for studying access to medicines, which makes it a critical tool for measuring health system performance and outcomes [4].

The United Nations' Sustainable Development Goals (SDGs) has given central attention to health (SDG 3) to "ensure healthy lives and promote well-being for all at all ages" and "focus on improving equity to meet the needs of women, children and disadvantaged populations in particular so that no one is left behind" [6]. Access to medicines is highlighted in the SDGs as an important component of UHC [2, 7]. In this thesis, I focus on the access to and use of medicines among two populations: Syrian asylum seekers and refugees in Germany, and the population in Syria with government health insurance. Although both groups are covered by health systems that grant them access to healthcare services, including medicines, their access is limited due to different barriers and challenges, which I will present in the following sections of this thesis.

2.1. Syrian asylum seekers and refugees in Germany

2.1.1 Asylum seekers and refugees in Germany and globally

An asylum seeker is "an individual who is seeking international protection and whose claim has not yet been finally decided on by the country in which the claim is submitted" [8]. A refugee, according to the 1951 Geneva refugee convention, is "someone who is unable or unwilling to return to their country of origin owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion" [9].

War, conflict, human rights violations, and disasters worldwide has forced people to flee their homes. The United Nations High Commissioner for Refugees (UNHCR) has estimated that the number of displaced people reached 84 million by mid-2021. Globally, Syrians currently form the largest group of refugees (6.8 million) followed by refugees from Venezuela (4.1 M), Afghanistan (2.6 M) and South Sudan (2.2 M). [10]. The majority of refugees (83%) live in countries neighboring their countries of origin [11]. This is reflected by the higher numbers of refugees in countries neighboring conflict zones, with Turkey hosting the highest number of refugees (3.7 M), followed by Colombia (1.7 M) Uganda (1.5 M) and Pakistan (1.4 M) [10]. With 1.2 M refugees, Germany hosts the fifth largest group worldwide, and the largest group of refugees in Europe. Syrians constitute the largest group of the total asylum seeker and refugee population in Germany (42%) [10, 12]. In 2015 The number of asylum seekers and refugees hosted by 28 EU member states, including Germany, has reached 1.3 million. This number is low considering the recent global trend of forced migration. Turkey alone hosted 3.4 million refugees, Pakistan and Uganda hosted 1.4 million each during 2015 [13–15]. However, the phrase “refugee crises” has frequently been in the public discourse since the peak of forced migration in 2015. The issue of migration has become an essential part of political debates in both Germany and other European countries [15, 16].

2.1.2. Access to healthcare services among asylum seekers and refugees in Germany

The right to health is a fundamental human right, and the right to access healthcare for refugees is anchored in the 1951 Refugee Convention [17]. The inclusion of refugees in national health systems is a priority of the UNHCR, the UN agency that is “...dedicated to saving lives, protecting rights and building a better future for refugees, forcibly displaced communities and stateless people” [18]. Thus, including refugees in national health systems is in line with the Global Compact on Refugees and the 2030 UN Agenda for Sustainable Development [17].

Germany joined the Geneva Refugee Convention in December 1953 and is still a party to the agreement [19]. Since then, refugees have been entitled to access regular healthcare services in Germany. Asylum seekers were also entitled to access the regular healthcare services until 1993 [20–22]. However, since 1993, the German government has restricted asylum-seekers’ access to welfare benefits, including healthcare, by introducing the asylum seekers benefit act

(Asylbewerberleistungsgesetz, AsylbLG) [21]. Articles 4 and 6 of this act state that asylum seekers are entitled to emergency medical care, treatment for acute and painful conditions, care during pregnancy and childbirth, vaccinations, and other “necessary preventive measures”. Asylum seekers are also entitled to additional care in instances that could be evaluated or approved to be essential for the preservation of health [23].

In Germany, there is a copayment for prescription medicines. Statutory insured persons pay 10% of the sales price per each prescription medicine, up to a maximum of ten euros and a minimum of five euros. Children under 18 years of age are exempt from all co-payments. Over-the-counter (OTC) medicines are not typically reimbursed by statutory health insurance. This exemption does not apply to children under the age of 12 and adolescents up to the age of 18 with developmental disorders. Doctor-prescribed OTC medicines for these groups will be reimbursed [24]. These regulations also apply to refugees and to asylum seekers who have been waiting more than 15 months for a decision by the migration authorities on their asylum application. Asylum seekers are exempt from copayments for medicines if their application for asylum is less than 15 months old. However, these medicines need to be prescribed in the health insurance coverage scope, which is regulated by the AsylbLG. This includes medicines prescribed for acute and painful conditions or for the recovery of illnesses [21]. Expenditures on medicines among asylum seekers in Germany in 2016 were approximately half of what was spent on a matched group of statutory insured people [25].

The legal restrictions to accessing healthcare services among asylum seekers has often been criticized. While the aim of these restrictions was to reduce the budget spent on asylum seekers [26], there is quantitative evidence indicating that restricting access to healthcare for asylum seekers has not been cost-effective but, instead, more expensive than granting regular access [23]. The UN Committee on Economic, Social and Cultural Rights published its concluding observations on Germany in October 2018 and raised concerns regarding the restriction of healthcare access for asylum seekers in Germany to painful conditions for the first 15 months of their stay [27]. The UN Committee directly requested revisions to the AsylbLG to ensure that all individuals have equal access to curative, preventive, and palliative health services regardless of their legal status [27, 28]. Using a human rights perspective, Bozorgmehr et al. have argued that restricting access to healthcare among any population group based on their residency status can be regarded as a violation of the right to health [26].

The legal restrictions to accessing healthcare among asylum seekers are coupled with administrative barriers in some parts of Germany [23]. Before 2014, asylum seekers received quarterly renewable healthcare vouchers, which could be used for doctor's visits. However, they needed to make a personal request at a social welfare-office to obtain these vouchers [29]. This procedure has been criticized as social welfare-office employees do not typically have the relevant qualifications to make decisions regarding the need for medical treatment [30]. Following the arrival of a high number of asylum seekers in Germany in 2015, the Berlin senate introduced new health policies for asylum seekers to ease their access to healthcare. This included replacing the healthcare vouchers for asylum seekers with electronic health insurance cards (EHICs). This system has been already adopted by two states: Bremen and Hamburg [31, 32]. Governments of other states have also considered introducing EHICs to asylum seekers. In the debate surrounding whether states should make the policy change to EHICs, opponents have claimed that the insurance cards will lead to a loss of control over access to healthcare among asylum seekers, which would result in an overuse of health services and increases in government health expenditures on this group [31]. However, advocates of the policy of introducing the EHIC argue that it simplifies bureaucratic and administrative procedures [31, 33, 34]. Furthermore, there is no evidence that introducing EHICs for asylum seekers will lead to the overuse of health services and healthcare expenses. A study that investigated the effects of introducing these cards for asylum seekers in Berlin showed that the policy change led to several benefits to the local health system including reduced bureaucratic complexity and administrative workloads, and improved financial transparency and control. This study also documented a decrease in the expenses for outpatient healthcare provisions for asylum seekers after the introduction of the EHIC [31]. By the year 2021, the EHIC for asylum seekers had been introduced in six federal states in Germany: Bremen, Hamburg, Berlin, Schleswig-Holstein, Brandenburg, and Thuringia. The card has also been introduced in some municipalities in three other federal states (Lower Saxony, NRW, and Rhineland-Palatinate). In the remaining seven states (Bavaria, Baden-Württemberg, Saarland, Hesse, Saxony, Saxony-Anhalt and Mecklenburg-Western Pomerania) the EHIC for asylum seekers has not yet been introduced [32, 34].

2.1.3. Previous studies about the access to and use of medicines among asylum seekers and refugees in Germany and other countries

In addition to system-related restrictions or administrative barriers, studies have reported other obstacles that limit the access to medicines among asylum seekers and refugees in other countries such as Australia, United Kingdom and the United States. These include language barriers, and financial costs [35–38], all of which can affect the consumption of medicines [39]. Barriers to accessing medicines are of special relevance as they can affect patient safety and limit adherence to treatment regimens [37, 38]. There is a need of studies that provide an understanding of how these barriers impact the different subgroups of the asylum seekers and refugee populations and identify the subgroups that are more affected by these barriers. The outcome of these studies can support the development of recommendations and interventions to improve access to medicines among asylum seekers and refugees.

Cultural and religious beliefs can also have an effect on access to healthcare and treatment [40]. According to the Federal Office for Migration and Refugees, approximately 85% of Syrian nationals who applied for asylum in 2020 mentioned Islam as their religion [12]. Islam recommends avoiding the consumption of food or beverages that contain alcohol or pork products [41], both of which maybe present as active ingredients, e.g., porcine heparin, or excipients, e.g. ethanol in many pharmaceuticals, or pork gelatine in capsules [42]. There is a lack of information concerning acceptance of “Western medicine” among asylum seekers and refugees from the Middle East [38]. Therefore, in Study I, we presented a group of adult Syrian asylum seekers and refugees on their acceptance of taking medicines containing alcohol or pork products. The acceptance of taking medicines that contain pork products is an issue, not only for Muslim patients, but also for those of other religions such as Jews, or those who follow certain diets (vegans) [42]. Therefore, addressing the acceptance of using medicines that contain alcohol or pork products is relevant to different groups of any diverse society [43].

Research on the medical care and health status of asylum seekers and refugees in Germany largely focused on mental disorders and infectious diseases [44]. In a systematic review covering 25 years of publications on asylum seekers and refugees’ health, Bozorgmehr et al identified 52 articles of which 30 studies focused on mental disorders, 12 on infectious diseases, and six on access to healthcare services and mental disorders among children. One of the remaining four studies was a systematic review that also focused on mental disorders,

while the other three studies covered various topics, including access to healthcare services, mental disorders, infectious diseases and NCDs [45].

Little is known about the use of medicines among asylum seekers and refugees in Germany and in Europe [45, 46]. Kahl et al published two studies on prescription data among a sample of asylum seekers in one reception center in Erlangen, Bavaria [47, 48]. One of these studies focused on psychotropic medicines and the other on antibiotics. The authors did not provide either the reasons for prescribing medicines or the nationality or sex of their study population [47, 48]. Another study investigated healthcare utilization, including medicines use, among asylum seekers in Halle, Saxony- Anhalt [49]. These three studies included only prescribed medicines. None of them provided adequate information on the use of medicines for NCDs. When estimating medicine use rates in a given population all medicines should be considered, including those used by self-medication [50]. There is an urgent need for studies that describe the use of medicines, including all therapeutic classes among asylum seekers and refugees to prevent and treat various diseases, including NCDs [51]. These three studies were limited to newly arrived asylum seekers who live in refugee shared accommodation centers (RSACs) [47–49]. A study reported the use of medicines among Syrian asylum seekers in Norway. This study was also limited to newly arrived adult asylum seekers to their hosting country [46]. The duration of stay in a host country can play a role in the health status of asylum seekers and refugees. Over a longer period of stay, asylum seekers and refugees health profile tends to converge with that of the host country's population [52, 53]. Therefore, studies should consider including asylum seekers and refugees with long-term stays in hosting countries.

2.2. The population with government health insurance in Syria

2.2.1 Healthcare in Syria before the conflict

Before the onset of the conflict in 2011, the healthcare system in Syria was comparable to healthcare systems in other middle-income countries [54]. Over the three decades prior to the conflict, there was a considerable improvement of health indicators in Syria. Data from the Syrian Ministry of Health showed a decrease in infant mortality from 132 per 1000 live births in 1970 to 17.9 per 1000 live births in 2009. Maternal mortality dropped from 482 per 100,000 live births in 1970 to 52 per 100,000 live births in 2009, and there was an increase in life expectancy from 56 years in 1970 to 73 years in 2009 [55, 56]. Syria went through an

epidemiological transition from communicable to NCDs in the few decades before the conflict. In 2009, 77% of the mortalities in Syria were caused by NCDs [55, 56]. The Syrian Ministry of Health is responsible for the provision of healthcare services in the country, with 2.9% of government expenditure dedicated to financing healthcare, which is among the lowest in the Middle East [54, 56, 57]. The costs of outpatient consultations and medicines are commonly covered by out-of-pocket expenditures [58].

The healthcare system in Syria was increasingly privatized [59]. Poor leadership and governance by the Syrian Ministry of Health led to geographic inequalities and an imbalance between available healthcare services and the needs of the population. Moreover, the private healthcare sector was focused on major urban areas such as Aleppo, Damascus and Homs leaving rural areas neglected [54, 60].

The pharmaceutical sector in Syria developed successfully during the three decades prior to the current conflict [61, 62]. Syria relied almost entirely on importing medicines until the mid-1980s as only two laboratories—which were government-owned—produced 6% of the local market’s needs. However, there was subsequent growth in the Syrian pharmaceutical industry through an increase in investments by the private sector, which was encouraged by the government. By 2010, just before the war, the number of pharmaceutical factories had reached 63 and were producing 5,700 different types of products to cover nearly 90% of the national medicine needs in Syria [62].

2.2.2. Healthcare in Syria during the conflict

The civil movement that began in Syria in March 2011 as a part of the Arab spring turned, over time, to armed conflict [63]. This conflict led to a humanitarian disaster that has been described as the “worst man-made disaster since World War II” [63, 64]. In addition to the 6.8 million people who fled Syria, there are 6.2 million who are internally displaced and constitute the largest internally displaced population in the world [65]. The conflict has also led to a profound destruction of the healthcare system in Syria [63]. As an outcome of this conflict, Syria was among the four countries with the highest number of attacks targeting health workers that were recorded by the International Committee of the Red Cross in the years 2016-2020 [66]. These attacks led to the damage or destruction of approximately 50% of the healthcare facilities in Syria and the exodus of 70% of the healthcare workers [67]. This

destruction of the healthcare system has led to an increase in infectious and NCDs risks, conflict-related trauma, serious maternal and child health challenges, and mental health issues [63, 68].

The healthcare system in Syria has been fragmented into at least four subnational healthcare systems as an outcome of the conflict and various geopolitical and humanitarian drivers [59, 69]. The following were the main subnational health systems in 2021 (Figure 1):

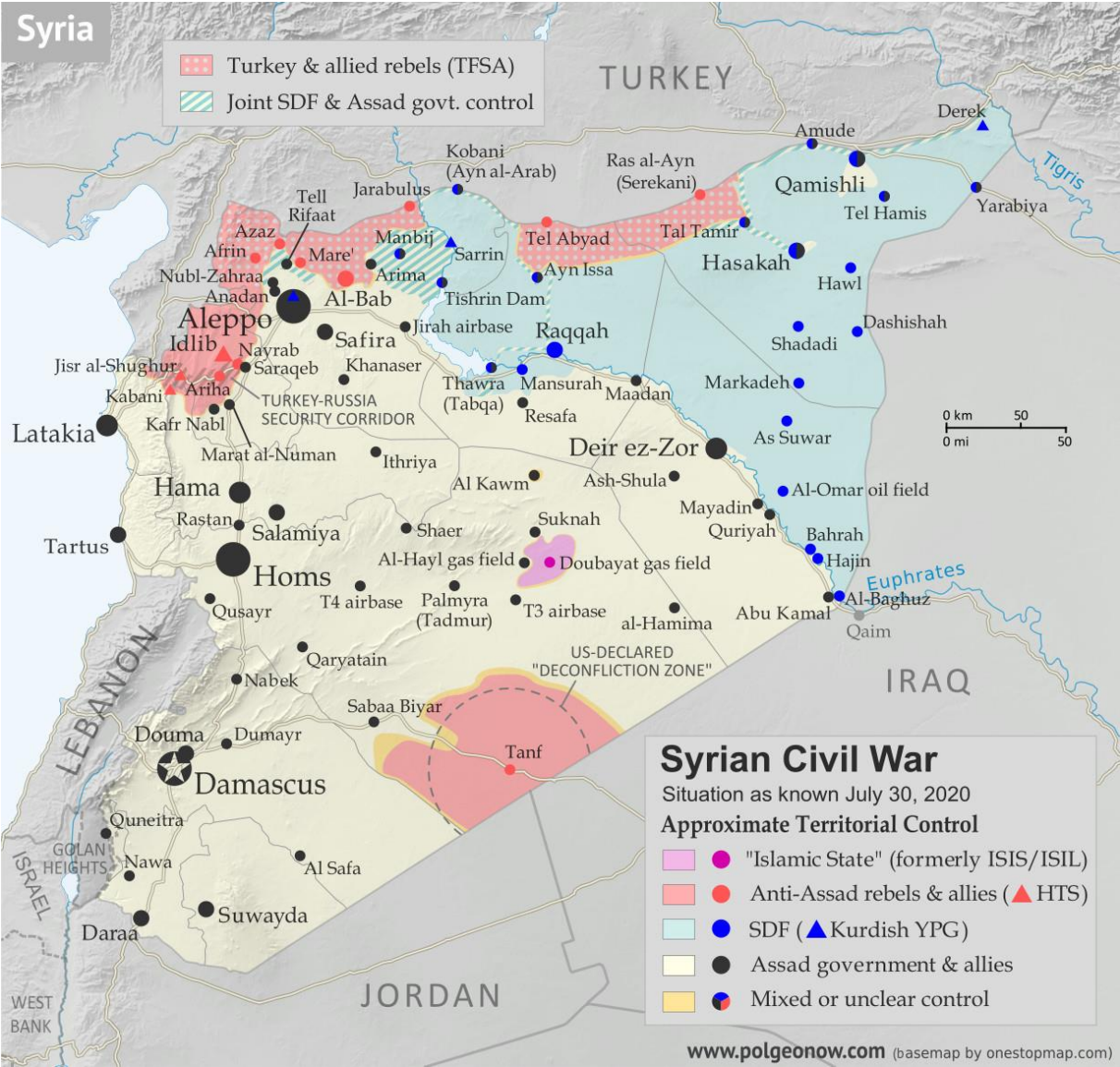


Figure 1 Control of various Syrian territories in 2020.

Source: "Syria Control Map & Report: Frontlines Stable—July 2020." 2020. by Evan Centanni and Djordje Djukic. Political Geography Now. <https://www.polgeonow.com/2020/07/syria-controlled-areas-map-2020.html>.

- Areas controlled by the Syrian government, which account for two-thirds of the country. In these areas, healthcare services are provided by the Syrian Ministry of Health.
- Areas under the Autonomous Administration of North and East Syria, which include parts of Al-Hasakah, Ar-Raqqa, Deer el-Zour, and the Aleppo governorates.
- Areas under opposition control that include the northern Idlib governorate, parts of Aleppo, and the northwest Hama governorates.
- Areas under Turkish control, which include the northern area of the Aleppo governorate that is along the Turkish border. In this area, healthcare services are provided by the Turkish Ministry of Health [59].

2.2.3. Health insurance in Syria

There is no national health insurance that covers all the inhabitants of Syria. However, members of professional associations and individuals working in public organizations are provided with health insurance [57]. Starting in 2004, private insurance companies have provided individual and group health plans [70]. A total of 926,252 individuals were covered by health insurance in Syria in 2020, with approximately 77% of the insured employed by the government [71]. This includes employees who occupy a variety of positions such as public-school teachers, administrative staff, and janitors. The diagnoses and treatment of various diseases, including CVDs and diabetes, are covered by government health insurance. However, this does not cover all diseases. For instance, chemotherapy and cancer radiotherapy, the treatment costs of some chronic conditions such as Parkinson's disease and Alzheimer's are not covered. Moreover, health insurance does not cover the treatment costs of war injuries or injuries resulting from harmful radiation and chemical or nuclear contamination, or the treatment of psychiatric illnesses or sexually transmitted diseases [72].

2.2.4. Previous studies about the use of medicines in Syria

The conflict in Syria has influenced the rates, and topics of health-related research there. Approximately 72% of the total health-related articles on Syria (between 1991-2017) were published after the start of the conflict in 2011. These articles mainly focused on mental health, accidents, injuries, and conflict and health [63]. In an assessment of the gaps in information and the need for research that focuses on conflict-related population health in

Syria, The Lancet-American University of Beirut Commission on Syria identified gaps in research regarding major components of the healthcare system, such as essential medicines. The commission called for research that addresses these knowledge gaps to provide evidence, inform policy, and support efforts that are required to protect and promote health in Syria [73].

Studies III and IV were the first studies to report about the dispensing of various groups of medicines at the population level in Syria using health insurance data from a large sample (81,314 beneficiaries) over a 12-month period. Study III reported antibiotic dispensing. While Study IV focused on CVDs and diabetes medicines dispensing. The justification for focusing on these groups of medicines is following the increase in the risk of infectious disease transmission resulted from the destruction of the healthcare system caused by the conflict in Syria [74, 75]. The ongoing conflict situation in Syria has increased the prevalence of penetrating traumatic injuries with contaminated open wounds and fractures as well as the increased spread of infections [76]. Ensuring antibiotic access in armed conflict settings is necessary to treat these injuries and to control the spread of diseases [77]. However, the use, including the misuse and overuse, of antibiotics is one of the main factors contributing to the development of antibiotic resistance. This has reduced treatment options for infectious diseases, hence, jeopardizing global public health [77, 78]. Studies have reported high rates of antibiotic resistance in Syria. However, insufficient data are available regarding the rates and patterns of antibiotic consumption [76, 79]. Few studies have examined access to antibiotics without prescription in Syria. These studies were limited to certain settings, such as universities and larger urban areas, e.g., Aleppo and Damascus [80–82]. None described the patterns or calculated the quantities of used or dispensed antibiotics. A Report from Yemen, a country effected by an ongoing conflict, showed how antibiotics were excessively used creating challenges of treating war wounds infected by bacteria that were resistant to several antibiotics [83]. Reporting data on antibiotic use is a cornerstone of antibiotic stewardship programs [84]. Médecins Sans Frontières has created a multifaceted, context-adapted, field experience-based, approach to antimicrobial resistance in hospitals in Middle Eastern conflict settings. This approach focused on three pillars. Antibiotic stewardship was one of these three pillars [85].

People with chronic diseases such as diabetes face numerous challenges during periods of conflict. These include inadequate access to medicines and testing supplies, and food insecurity [86]. During humanitarian crises and in conflict zones, the distribution of medicines can be challenging due to political and geographical barriers, even if they were available [86]. In 2018, a study conducted among a group of diabetes patients in a public hospital in Damascus reported that 74.8% of these patients attributed stopping their therapy to the unavailability of medicines, and 41.2% of these patients had stopped their medicines for at least one month over the course of seven years of conflict. Because of the closure of many pharmaceutical companies due to the conflict, half of the patients had to change their medicines brand names [87]. Despite the high prevalence of CVDs and diabetes in Syria, little is known about medicines utilization or prescriptions for these diseases [88]. Therefore, Study IV has focused on CVDs and diabetes medicines dispensing among patients with government health insurance in Syria.

3. Aims

The overarching aim of this doctoral thesis is to describe drug utilization among two populations: asylum seekers and refugees in the German Federal state of NRW, and a population with government health insurance in Syria.

This thesis comprises four studies with the following specific aims:

- To describe and understand barriers to accessing medicines among Syrian asylum seekers and refugees and to provide an understanding of their perspectives towards taking medicines that contain alcohol or pork products. This includes any differences between sex and age groups or between participants with and without chronic diseases in their experiences accessing medicines. *(Study I)*
- To examine the prevalence and patterns of medicine use and to document self-reported diseases or conditions for which medicines were used among Syrian asylum seekers and refugees. This includes investigating differences in the use of medicines between sex and age groups of the study participants. *(Study II)*

- To examine the rates and patterns of dispensing outpatient antibiotics among those with government health insurance in Syria and to explore differences in the rates of antibiotic dispensing between different sex and age groups of this population and assess regional and seasonal variation in antibiotic dispensing. (*Study III*)
- To examine the patterns and rates of dispensing medicines used for CVDs and diabetes among patients with government health insurance in Syria and to explore age, sex, and regional variations in the dispensing of these medicines. (*Study IV*)

4. Material and methods

4.1. Drug utilization research

Drug utilization research is defined as “an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes” [4]. Drug utilization research is linked to health services research, since the drug utilization studies aim to improve medicines use. Drug utilization research is also related to the disciplines of pharmacoepidemiology and clinical pharmacology [4].

Research methods applied in drug utilization studies can be broadly categorized as either quantitative or qualitative. Quantitative methods are typically used to measure, explain, predict, or generalize observations [4]. In drug utilization research, these methods are typically used to report patterns or trends and provide a deeper understanding of the factors behind drug utilization patterns [4]. In contrast, qualitative research methods include collecting, analyzing, and interpreting information that is not in numerical form for a better understanding of various phenomena [4]. In drug utilization research, qualitative methods are usually employed in analytical drug utilization studies and are used to gain insight into patient and prescriber perspectives [4]. This thesis is primarily based on a quantitative methodology (Table 1). However, in Study I, the answers given by participants on an open-ended question yielded data that were analyzed using qualitative methods (thematic analysis). The qualitative data analysis in Study I supported the interpretation of the quantitative findings [43].

4.2. An overview of the included studies

Table 1: An overview of the studies included in this thesis

Study	I	II	III	IV
Design	Quantitative data, qualitative data, cross-sectional	Quantitative data, cross-sectional	Quantitative data, cross-sectional	Quantitative data, cross-sectional
Population	Syrian asylum seekers and refugees in Germany, all age groups	Syrian asylum seekers and refugees in Germany, all age groups	The population with government health insurance in Syria, adults only (≥ 18)	The population with government health insurance in Syria, adults only (≥ 18)
Data source	Patient-reported data (questionnaire)	Patient-reported data (questionnaire)	Outpatient dispensing data	Outpatient dispensing data
Study period	July-December 2019	July-December 2019	June 2018-May 2019	June 2018-May 2019
Main factors analyzed	Barriers to accessing medicines, perspectives towards taking medicines that contain alcohol or pork products	Prevalence and patterns of medicine use, self-reported diseases or conditions that led to medicine use	Patterns and rates of antibiotic dispensing	Patterns and rates of CVDs and diabetes medicine dispensing
Statistical analyses	Nonparametric analyses: Mann–Whitney U test and Kruskal–Wallis ANOVA	Pearson’s χ^2 test	Nonparametric analyses: Mann–Whitney U test and Kruskal–Wallis ANOVA	Nonparametric analyses: Mann–Whitney U test and Kruskal–Wallis ANOVA

4.3. Data sources in drug utilization research

A wide variety of data sources are used in drug utilization research and can be mainly classified as primary or secondary data sources [4].

4.3.1. Primary data

Primary data are original data that have been collected to answer specific research questions. These data have never been previously collected or structured to be accessible for research [4]. Primary data collection in drug utilization research may involve individuals (e.g., patients, physicians, pharmacists, nurses, and stakeholders) and documents (e.g., prescriptions, and laboratory data). Primary data are usually collected through standardized and structured questionnaires or forms designed for data extraction [4].

In Germany and many European countries, nationwide data that report on the health and care of asylum seekers and refugees are non-existent. Therefore, researchers who are interested in conducting health research studies, including drug utilization research, among asylum seekers and refugees need to collect primary data [89–91]. Studies I and II are based on primary patient-reported data collected via a structured questionnaire. Through this questionnaire we collected data on barriers limiting access to medicines among Syrian asylum seekers and refugees in Germany (Study I), as well as the patterns and rates of medicines used and the diagnoses that led to using these medicines (Study II).

Patient-reported data such as questionnaires have several advantages (Table 2). As primary data, they can provide researchers with the relevant information they need to answer research questions that might not be included in recorded secondary data (such as information about the patient's experiences and attitudes). In addition, patient-reported data provide information about OTC-medicine use that is not available in some secondary data sources such as prescription or dispensing data. As patients are drugs' end users, patient-reported data are close to estimating actual drug utilization because it generally documents all drugs used despite whether they were prescribed or obtained OTC [4]. This also includes medicines shared with others. However, patient-reported data have a number of limitations. These include being time and cost consuming. Furthermore, large-sample data collections can be challenging and rare [4]. Other disadvantages of patient-reported data include being prone to recall and reporting bias, misinterpretation, misinformation, and nonresponses [4]. Therefore, careful development of the questionnaires and recruiting strategies used for data collection is critical to reducing the effect of these challenges [4].

4.3.2. Secondary data

Secondary data are routinely collected for administrative purposes. They are also usually gathered as part of patient care. While they are not collected for a specific research purpose, they can be applied or analyzed to answer new research questions [4].

An overview of the different steps that lead to generating secondary data in drug utilization research can be achieved by considering the several steps in the context of the pharmaceutical supply chain, which start with the manufacturer and conclude with the patient [4]. Here we can categorize secondary data into two major groups:

- Aggregate-level data: These include manufacturer and wholesaler data and reflect the total amount of drugs in a certain system.
- Individual-level data: These provide information about drug utilization at the individual level and include pharmacy and hospital sales or dispensing data as well as data reported by healthcare providers and from patient registries and population health surveys.

Studies III and IV of this thesis were based on data acquired from a health insurance provider that recorded prescribed medicines dispensed for outpatient care in Syria.

Outpatient dispensing data have several advantages (Table 2). First, they can provide information about drug utilization in a large sample at lower cost and a shorter time period compared to primary data. Second, the medicines included in dispensing data are those that have been purchased and not simply prescribed [4]. Therefore, as opposed to other sources of secondary data, they are closer to the actual exposure to medicines among patients [4]. However, there are limitations related to the application of dispensing data in drug utilization research. These data usually lack information concerning confounders such as lifestyle factors or socioeconomic status. The dispensing data used in Studies III and IV did not include information on the diagnoses that led to prescribing the recorded medicines. In addition, dispensed medicines that were recorded were not necessarily used. Furthermore, many outpatient dispensing data only included information about medicines dispensed within the reimbursement system [92]. Medicines dispensed in hospitals would not typically be included in a database focused on outpatient dispensed medicines [4].

Table 2: The advantages and limitations of the data sources used in the studies.

Data sources	Advantages	Limitations
Person-reported data (Questionnaire)	Primary patient data, data on different variables of interest are collected, reflect actual medicine use, include all medicines (prescribed and self-medication)	Time and cost-consuming, small sample, recall bias
Outpatient dispensing data	Large sample, low cost, drugs are purchased and not only prescribed	Many confounders are not included, no information about self-medication or medicines administered at hospitals

4.4. Main factors analyzed

4.4.1. Barriers to accessing medicines among Syrian asylum seekers and refugees (Study I)

The questionnaire used in Study I contained items that were categorized into two groups of questions. One group included questions about the barriers asylum seekers and refugees encountered when accessing medicines. These questions focused on the effects of the following four factors on access to medicines: (1) language barriers, (2) the availability of certain medicines in German pharmacies, (3) financial barriers and, (4) the possibility of purchasing medicines without a prescription. These factors were chosen based on information from previous studies that focused on barriers to accessing healthcare services or medicines among refugees or migrants in different countries including Australia, United Kingdom and the United States [35, 37, 38] and on the perspectives of Syrian asylum seekers and refugees who were involved in developing the questionnaire for this study [43]. Participants were asked to answer questions about the effect of these factors on their access to medicines on a scale from 1 to 7 (1 = No effect at all, 7 = Very large effect). The second group of questions focused on the acceptance towards taking any medicine that contained alcohol or pork products. The decision to address this topic was based on the suggestion of Syrian asylum seekers and refugees who were involved in developing the questionnaire for the study [43]. In addition,

we have searched for studies about the perspective of migrants or refugees in Germany or Europe towards taking medicines that contain alcohol or pork products and noticed that this issue has been understudied.

4.4.2. Medicine use among Syrian asylum seekers and refugees (Study II)

Our questionnaire included questions from the German Health Interview and Examination Survey for Adults (DEGS) [93] and the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [94]. The DEGS and KiGGS are national representative surveys that the Robert Koch Institute, the leading national health institute in Germany, has regularly conducted since 2003 and 2008. For collecting data about medicine use, we recorded the brand name, the international non-proprietary name, and the pharmaceutical dosage for each medicine a respondent mentioned using. In addition, we recorded the reason for taking the medicine, the number of daily doses, the intake duration, the medicine administration route, and how it was obtained [44].

We used the World Health Organization's (WHO's) Anatomical Therapeutic Chemical (ATC) Classification system (2020 version) to classify the medicines reported in Study II [95]. Medicine consumption per therapeutic group was expressed in two ways: as the total number of doses for each medicine and as the seven-day prevalence in adults and children. The seven-day prevalence of medicines use in Study II was calculated as the proportion of asylum seekers and refugees who had used at least one medicine in the seven days preceding data collection [44]. We presented the relative use of medicines by stratifying the total amount of medicines used by sex and age. We also reported the number of DDDs for each medicine reported by adult participants. DDD was defined as: "the assumed average maintenance dose per day for a drug used for its main indication in adults" [95]. The number of DDDs was calculated based on medicine use in adults [95]. Among children and adolescent participants, the number of packages was used as the measurement unit for medicine consumption, as DDD is not appropriate for those age groups [4, 96].

4.4.3. Outpatient medicine dispensing (Studies III and IV)

In Studies III and IV, we used the ATC/DDD (version 2020) methodology to analyze dispensed medicines. The rates of dispensed medicines were expressed as the number of DIDs. The DID is a measurement that is frequently used in drug utilization research studies to control for

changes or differences in population size between or within countries [4]. We grouped medicines using the ATC classification. Study III included medicines classified as J01 (antibacterials for systemic use). Study IV included CVDs and diabetes medicines. CVDs medicines were classified under those from groups C (cardiovascular system) and B01 (antithrombotic agents) of the ATC classification. Diabetes medicines included those from group A10 (drugs used for diabetes). We adjusted the number of DIDs according to patient sex and age using the number of beneficiaries in each sex and age group [44]. This number was available through the dispensing data. To assess regional variation in medicine dispensing in Studies III and IV, we adjusted medicine dispensing rates according to governorates by calculating the number of DDDs per 1000 medicine dispensing events per day (DDED). In Study III, the relative dispensing of antibiotics was presented as a percentage of the total dispensing by route of administration (oral or parenteral) and AWaRe (Access, Watch and Reserve) categories [78]. The WHO AWaRe classification of antibiotics was developed as a “tool to support antibiotic stewardship efforts at local, national and global levels” [97, 98].

4.5. Patient and public involvement

To address the challenges associated with conducting research with asylum seekers and refugees and enhance our understanding of the subject matter, we involved Syrian activists and other prominent members of the Syrian community in the state of NRW who voluntarily took part in different stages of Studies I and II (including the studies’ planning, execution, and analysis). During the development of the questionnaire used for both studies, they provided comments and suggestions for the questions that were included and on their translations. Their support was especially important during the recruitment of study participants as they suggested places and locations where we could recruit participants [43, 44]. In addition, they gave feedback on the findings and recommendations of the research. In Studies III and IV, few Syrian nationals provided comments and feedback on the findings and outcome of those studies.

4.6. Ethical considerations

Research studies that include asylum seekers and refugee populations should adhere to ethics guidelines that apply to studies of any population. Numerous factors make refugees more vulnerable to research-related harm than other populations. These include several challenges

related to their experiences in their countries of origin, during their forced migration, or in the hosting countries. Researchers interested in conducting studies that include asylum seeker and refugee populations should be aware of these factors during the planning and implementation of their research. It is equally relevant that the institutions involved in the study including the institutional review boards are equipped with handling the review and approval of the research.

Refugees often differ from non-refugees in the degree of political protections or types of social services offered to them. Migration is a politicized issue; therefore, the way ethics principles are applied and the emphasis given to certain principles should be specific to the refugees' circumstances [99, 100].

For Studies I and II, informed consent was obtained from respondents after introducing the study in clear language. We explained that participation was voluntary, and that participating or refusing to participate in the study would not have any effect on the legal status of the potential participant and that the questionnaire would not include any questions that could lead to identifying the person who answered the questionnaire. Prior to our field study, we secured the approval of the ethics committee of the University of Bayreuth (Protocol code O 1305/1-GB. Date of approval: 21.05.2019) [43, 44].

For Studies III and IV, we used an anonymized database. It was not possible to identify any patient through the information included in these data. The ethics committee of the University of Bayreuth stated that the analysis and reporting of the dispensing data in this study did not require their approval [78, 101].

5. Summary of the results

5.1. General characteristics of the studies populations

A total of 1,641 Syrian asylum and refugees were included in Studies I and II. Of these, 1,063 were adults (≥ 18 years), 456 were children (≤ 13 years) for whom one parent answered the questions for them, and 122 were adolescents (14–17 years). Males comprised 62.4% of the participants. Table 3 lists the sociodemographic characteristics of the participants.

Table 3. Sociodemographic characteristics of the participants in Studies I and II.

Participant characteristics	Number of participants	Proportion (%)
Sex		
Male	1024	62.4%
Female	617	37.6%
Age		
0–17	578	35.2%
18–29	468	28.5%
30–39	318	19.4%
40–49	158	9.6%
50–59	78	4.8%
60>=	41	2.5%
Health insurance		
Yes	1616	98.5%
No	23	1.4%
Missing	2	0.1%
Residency status		
Refugee status or subsidiary protection	1603	97.7%
Asylum seeker	38	2.3%
Accommodation		
Initial reception center	18	1.1%
Long-term accommodation center	318	19.4%
Private housing	1289	78.6%
Missing	16	0.9%
Chronic disease (Adults only)		
Yes (22 different chronic diseases)	146	13.7%
No	914	86.0%
Missing	3	0.3%
The most common chronic diseases		
Hypertension	71	6.7%
Diabetes	44	4.1%
Hypothyroidism	30	2.8%
Hyperlipoproteinemia	21	2.0%
Anemia	21	2.0%
Other chronic diseases	66	6.2%
Employment (Adults only)		
Employed	249	23.4%
Retired	16	1.5%
Vocational training	237	22.3%
Unemployed	537	50.5%
Missing	24	2.3%
German language level¹		
A1-A1	242	22.8%
B1-B2	495	46.6%
C1-C2	168	15.8%

None	131	12.3%
Missing	27	2.5%
Marital status (Adults only)		
Single	381	35.8%
Married	613	57.7%
In a relationship	27	2.5%
Divorced	19	1.8%
Widowed	13	1.2%
Missing	10	0.9%

¹Language levels were classified according to the Common European Framework of Reference for Languages (CEFR) [102].

Studies III and IV used the outpatient medicine dispensing data of 81,314 adult beneficiaries who were covered by government health insurance in Syria. The median age of the beneficiaries was 47 years (interquartile range: 37–56), and 50,643 beneficiaries (62.3%) were female while 30,671 (37.7%) were male. Table 4 lists the characteristics of Studies III and IV population.

Table 4. Characteristics of Studies III and IV population by age and sex.

Age group	Female		Male		Total	
	n	%	n	%	n	%
18–29	5,257	6.5	2,861	3.5	8,118	10.0
30–39	13,180	16.2	4,603	5.7	17,783	21.9
40–49	12,372	15.2	8,299	10.2	20,671	25.4
50–59	13,189	16.2	8,741	10.8	21,930	27.0
60–69	5,733	7.1	4,311	5.3	10,044	12.3
70≤	912	1.1	1,856	2.3	2,768	3.4
Total	50,643	62.3	30,671	37.7	81,314	100

5.2. Study I

Language barriers had the strongest effect on accessing medicines among adult and parental respondents. This was followed by barriers related to purchasing a medicine without a prescription. Among adult participants, financial barriers and the unavailability of certain medicines in German pharmacies had the lowest effect.

In regard to language barriers, there was a statistically significant difference ($p < 0.001$) between adult males and females, with a stronger effect observed in females. A statistically significant difference ($p < 0.05$) between adult age groups was found in relation to access to medicines and language barriers, financial barriers, and purchasing medicines without a prescription. The effects of these factors were stronger in those older than 50 years of age. There was also a statistically significant difference ($p < 0.001$) between participants with and without chronic diseases. Those with chronic diseases had a higher probability to report language barriers, financial barriers, and barriers in purchasing medicines without prescription on their access to medicines [43].

Approximately, half of the observations regarding the acceptance of taking medicines that contain alcohol or pork products among adults were above the median value of 4 (1–7) on a scale of 1–7. There was a statistically significant difference between male and female participants regarding taking medicines containing alcohol or pork products. Male participants displayed more acceptance than females. There was a significant difference between the different age groups. Participants younger than 50 years old were more accepting of these medicines than older participants. Participants with chronic diseases showed more acceptance towards taking medicines that contain alcohol or pork products. In addition, we observed that some participant subgroups showed more acceptance towards taking a medicine with alcohol than with pork products. Ninety-seven participants provided answers to an open-ended question regarding their perspectives and experiences accessing and using medicines. Some participants explained how they overcame language barriers, which usually entailed having a family member accompany them to doctors or pharmacies: “Sometimes when I go to the doctor, my daughter comes with me to translate for me.” One participant suggested that pharmacists should hand out an Arabic version of a medicine’s leaflet to help overcome the language barrier [43].

More details concerning the barriers to accessing medicines among Syrian asylum seekers and refugees in Germany can be found in Study I.

5.3. Study II

The seven-day prevalence of using at least one medicine was 41.4% among adult participants. A total of 6,466 doses of 951 medicines had been taken in the seven days preceding data

collection. The prevalence of medicine use was higher among females (46.6%) than males (38.8%) and increased with increasing age. The lowest prevalence was among adults between 18 and 29 years (27.1%), and the highest was among those ≥ 60 years (85.4%). The highest prevalence of medicine use (14.6%) was for medicines for the alimentary tract and metabolism (ATC code A); this was followed by medicines of the musculoskeletal system (M) (13.4%), the nervous system (N) (12.4%) and the cardiovascular system (C) (8.0%).

The prevalence of using at least one medicine was 18.5% among children. In total, 738 doses of 135 medicines had been taken by children in the seven days preceding data collection. The seven-day prevalence of medicine use was higher among girls (22.6%) than boys (15.0%). Unlike the adults, the highest prevalence of medicine use was among the youngest group of children (0–4 years). The prevalence of group M medicine use was the highest (8.1%), followed by those in the respiratory system (ATC code R) (4.7%), and the medicines of groups N and A (3.5% and 2.6%, respectively) [44].

Headache was the most commonly reported reason for taking medicines (8.4%) among adult asylum seekers and refugees, followed by hypertension (6.7%). The greatest number of individual doses of medicine were for hypertension (954 doses) and diabetes (595 doses). Four of the ten most commonly reported reasons for medicine use were chronic conditions: hypertension, diabetes, stroke prevention, and hypothyroidism. Among the ten most common conditions that led to medicine use, one was infectious (influenza) while none were psychiatric disorders. Seventeen adults (1.6%) reported taking 181 doses of 21 psychotropic medicines for psychiatric illnesses [44].

Fever (5.5%) and cough (4.0%) were the most common conditions that led to medicine use among children. Medicine use for chronic diseases among children was low (1.6%) with only two of the top ten causes for medicine being chronic diseases (epilepsy and asthma). Four of the remaining eight most frequent causes of medicine use were infectious diseases (influenza, cough, common cold, and otitis media). None of the children took medicine to treat psychiatric illnesses [44].

Details on the patterns and rates of medicine use among Syrian asylum seekers and refugees can be found in Study II.

5.4. Outpatient medicine dispensing among the population with government health insurance in Syria

In the 12-month period from June 2018 to May 2019, 46,281 beneficiaries (56.9%) received at least one medicine. The total number of DIDs dispensed for these patients was 591.2. Considering the number of DIDs, medicines in main anatomical group C (the cardiovascular system) of the ATC classification system were the most dispensed (35.8%), followed by those in group A (the alimentary tract and metabolism) (22.4%). Medicines in group J (anti-infectives for systematic use) were the sixth most commonly dispensed (3.5%).

5.4.1. Study III

Of the 33,444 patients who received at least one antibiotic as an outpatient, 11,061 (33.1%) were male and 22,383 (66.9%) were female. The total number of the DDDs of outpatient dispensed antibiotics was 59,7518.8, and the total number of the DIDs of outpatient dispensed antibiotics was 20.1. Amoxicillin + clavulanic acid (5.8 DID) was the most frequently dispensed antibiotic, followed by clarithromycin (4.4 DID).

The antibiotics in the Watch category of the AWaRe classification scheme had the highest percentage of dispensed antibiotics in this study (65.9%), followed by Access antibiotics (32.5%). Antibiotics in the Reserve category had the smallest percentage (0.8%). The remaining antibiotics (0.8%) were not classified. Considering the number of packages, 85% of the dispensed antibiotics in this study were for oral administration. The remaining 15% were parenteral. The dispensing data included seven fixed-dose antibiotic combinations, which accounted for 29.6% of the total dispensed antibiotics. Three of these fixed-dose combinations were listed in the Access group of the AWaRe classification system, while the remaining four combinations were not included in the AWaRe classification. These were: Ceftriaxone + Sulbactam, Amoxicillin + Flucloxacillin, Spiramycin + Metronidazole and Ampicillin + Cloxacillin. The WHO does not recommend the use of these four fixed-dose combinations in clinical practice, as the use of these four fixed-dose combinations of multiple broad-spectrum antibiotics is neither evidence-based nor recommended in high-quality international guidelines [98].

A statistically significant difference was observed in the antibiotic dispensing rates between male and female patients ($p = 0.003$). The adjusted DID rates of antibiotic dispensing were

higher among female patients (21.6 DID) than male patients (17.8 DID). A significant difference was also observed in the antibiotic dispensing rates between different age groups ($p < 0.001$). Adjusted antibiotic dispensing rates were the highest among patients aged 30–39 (25.1 DID) and the lowest was among patients aged 60–69 (14.4 DID).

During the study period, a statistically significant difference ($p < 0.001$) in the total antibiotic dispensing rate was observed between Syria's different governorates under the Syrian government's control. According to the number of DDEDs in each governorate, Idlib (16.3 DDED), Quneitra (14.6 DDED), and Deer el-Zour (14.3 DDED) had the highest antibiotic dispensing rates, while Tartous (5.8 DDED), Latakia (4.5 DDED), and Al-Suwayda (3.6 DDED) had the lowest rates [78].

5.4.2. Study IV

Of the total number of beneficiaries, 14,523 patients (17.8%) received medicines used for the cardiovascular system (C) and antithrombotic agents (B01). A total of 4,466 patients (5.5%) received diabetes medicines (medicines used in diabetes: A10). Only 0.14% of the beneficiaries received 0.96 DID of the A10A group (insulin and analogues). A total of 8,384 female beneficiaries (16.1%) and 6,141 (19.7%) male beneficiaries received outpatient CVDs medicines. The adjusted DID rates of CVDs medicines were higher among male patients (388.8 DIDs) than females (249.6 DIDs). This difference was statistically significant ($p < 0.001$) [101].

A total of 2,489 (4.91%) female beneficiaries and 1,977 (6.5%) male beneficiaries received outpatient diabetes medicines. The adjusted DID rates of diabetes medicines was higher among males (46.0 DIDs) than females (29.4 DIDs), and this difference was statistically significant ($p < 0.001$). Only 0.6% of the beneficiaries in the age group 18–29 received diabetes medicines. This proportion increased with age to reach 21.5% in the $70 \leq$ age group. The adjusted DID rates of diabetes medicines was the lowest in patients in the 18–29 age group (0.3 DIDs) and increased to 131.3 DIDs in the $70 \leq$ age group (Fig. 3). This difference was statistically significant ($p < 0.001$).

We found a significant difference ($p < 0.001$) in CVDs and diabetes medicine dispensing rates between Syria's different governorates. According to the number of DDEDs in each governorate, the Damascus countryside, Latakia, and Tartous governorates had the highest CVDs and diabetes medicine dispensing rates, while Deer el-Zour, Idlib, and Quneitra had the

lowest rates. The insurance data did not record insulin dispensing in the governorates of Al-Hasakah, Idlib, Deer el-Zour, or Daraa. Two of the three governorates with the highest CVDs and diabetes medicines dispensing rates (Latakia and Tartous) were among the three governorates with the lowest antibiotic dispensing rates. While, two of the three governorates with the lowest CVDs and diabetes medicines dispensing rates (Deer el-Zour and Idlib) were among the three governorates with the highest antibiotic dispensing rates [78, 101].

More information on CVD and diabetes medicine dispensing can be found in Study IV.

6. Discussion

6.1. Barriers to accessing medicines among Syrian asylum seekers and refugees in Germany (Study I)

To the best of our knowledge, Study I was the first study to investigate and report on the barriers to accessing medicines among a group of asylum seekers and refugees in Germany. The results of this study fill an important knowledge gap and support the development of recommendations to improve access to medicines for asylum seekers and refugees in Germany. Compared to the other three barriers we considered in this study; language barriers formed the major obstacle [43]. The result of Study I showed a significant difference between females and males concerning the effect of language barriers on access to medicines. This effect was stronger among females than males. In comparison to males, female refugees attend integration courses less frequently and with longer delays after their arrival in Germany. Female asylum seekers and refugees assessed their German language skills as weaker than males do [43]. This may be due to female refugees having fewer opportunities for using or practicing the German language. Female refugees who come to Germany with families often have less time to learn German as they tend to focus on childcare and housing provision [43, 103]. This is not a new phenomenon. Studies on refugees who arrived in Germany in the nineties also showed a slower integration of female refugees than their male counterparts [43, 103, 104].

There was a significant difference according to the effects of language barriers, financial barriers, and the possibility of purchasing a medicine without a prescription between participants from different age groups. Participants who were older than 50 years of age were more affected by these three factors. Older age is associated with a higher risk of chronic

diseases and higher medical referral rates [35, 43]. One study has shown that older refugees had higher unemployment rates, lower levels of education, and poorer language skills of the hosting countries compared to younger refugees [105]. Our qualitative analysis also demonstrated that some young respondents seldom acquired any medicines after their arrival to Germany due to their good general health status. This can explain why they were rarely confronted with the process of trying to get prescription medicine [43].

Study I has addressed an understudied issue: Acceptance towards taking medicines that contain alcohol or pork products among asylum seekers and refugees. We found a significant difference between female and male participants regarding their acceptance of taking medicines containing alcohol or pork products, with females being less accepting than males. There was also a significant difference between age groups. Those who were younger than 50 years of age showed more acceptance than those who were older. We do not have an explanation for these results and suggest that further qualitative studies are needed to explain them [43]. Our participants showed more acceptance towards taking medicines that contain alcohol than ones that contain pork products. Some Muslim countries accept or allow the use of medicines that contain alcohol (benzyl alcohol, methyl alcohol, and polyethylene alcohol) [106]. However, this does not apply to medicines contain pork products. Some schools of Islamic jurisprudence refuse to accept the use of medicines that contain pig gelatine even if it is highly purified and so degraded that the pig DNA cannot be detected, nor can the original source of the gelatine be identified [43, 107].

6.2. Medicine use among Syrian asylum seekers and refugees in Germany (Study II)

Considering the lack of routine reporting on the health status and quality of medical care, including medication use, among asylum seekers and refugees in Germany and the need for empirical studies to provide evidence to improve policy and clinical practice with this population [45], Study II provides an important contribution to our knowledge about medicines use among asylum seekers and refugees. This is the first study to report on medicine use (Prescribed medicines and self-medication) and indications among a group of asylum seekers and refugees in Germany [44].

Among adults, the use of medicines for NCDs was relatively common, with hypertension being the second-most common condition that led to medicine use. Treating hypertension and diabetes led to using the highest number of doses of medicine in the study period. These results are in line with studies that have reported high prevalence of both hypertension and diabetes among Syrian refugees in Turkey, Lebanon, Jordan and some countries in Europe [51, 53, 108].

Among the ten most common indications for medicine use, influenza was the only infectious disease. Amoxicillin was the only antibiotic among the 15 most commonly used medicines by adults. Kahl and Kühlein reported that Amoxicillin was the most commonly prescribed antibiotic for a group of asylum seekers in the city of Erlangen [48], Amoxicillin was also the most commonly prescribed antibiotic for Germans with statutory health insurance [109]. The low prevalence of medicine use for treating infectious diseases is in line with many other studies that reported the prevalence of infectious diseases among Syrian asylum seekers and refugees in Germany and other countries. One study reported a very low prevalence of tuberculosis among Syrian asylum seekers and refugees in Germany compared with asylum seekers and refugees from other nationalities [52, 110]. Another study that investigated the health status of asylum seekers and refugees in Bavaria reported a low prevalence of infectious diseases (4.8%) among Syrian asylum seekers and refugees [111].

Study II reported little use of antibiotics. This finding contrasts with findings of Kahl and Kühlein who reported a high proportion of antibiotic prescriptions for asylum seekers in Erlangen [44]. Kahl and Kühlein did not provide either the reasons for prescribing antibiotics or the nationality or sex of their study population [47, 48]. Factors such as country of origin have considerable effects on asylum seekers and refugees' health, and may account for our divergent findings [53]. Syrian asylum seekers and refugees present with different demographic profiles and disease burden than, for instance, asylum seekers and refugees from some African countries where a disease such as cholera would be more prevalent [51]. Another factor that could explain the differences between our results and those of Kahl and Kühlein may be due to their sample, which was limited to newly-arrived asylum seekers. In the sample of Kahl and Kühlein's study, the average period of stay in the reception center was 46.9 days. The average stay of Study II participants in Germany was 44.0 months [44]. Asylum seekers and refugees' duration of stay in a host country can play a role in their health status.

Over a longer period of stay, asylum seekers and refugees health profile tends to converge with that of the host country's population [52, 53].

The management of NCDs as hypertension and diabetes could pose a challenge for asylum seekers and refugees in many countries as they require adherence to continuous pharmacotherapy and frequent laboratory tests [112–115]. Currently, infectious diseases received the most attention of the clinical practice and policy related to asylum seekers and refugees compared with the management of NCDs [53]. In Germany, adult asylum seekers of all nationalities (except for pregnant women) are obliged to participate in chest X-ray screening for potentially infectious pulmonary tuberculosis [110]. Policies in Germany should account for the different regions where asylum seekers come from and the burden of diseases that could vary between these regions. Since 2015, the chest X-ray screening for Tuberculosis in the Netherlands was suspended for asylum seekers from countries with tuberculosis incidence (<50 cases per 100,000 people), such as Syria. This screening should be limited to asylum seekers from high-incidence countries to improve cost-effectiveness [44, 116]. The resources and efforts paid to X-ray screening for tuberculosis among Syrian asylum seekers can be invested instead in the management and prevention of NCDs [44].

6.3. Outpatient antibiotic dispensing among the population with government health insurance in Syria (Study III)

Study III provides the first estimates of outpatient antibiotics dispensing patterns and rates of a population with health insurance across areas controlled by the Syrian government. Study III reported high rates of outpatient antibiotic dispensing in Syria. Many studies have reported over-prescriptions of antibiotics in LMICs [117–119].

The outpatient dispensing of Watch antibiotics for the patients in this study was the highest (65.9%), followed by Access (32.5%) and Reserve antibiotics (0.8%). The remaining antibiotics (0.8%) were not classified. Comparing these results to those from three countries of the Eastern Mediterranean Region (Iran, Sudan and Jordan), we notice a larger share of the antibiotics was in the Access group in Sudan and in Iran (65.3% and 53.8% respectively), while the share of Access antibiotics was lower in Jordan (30.5%). The share of the Watch group antibiotics was larger in our study (65.9% in Study III vs 45.0% in Iran, 17.1% in Sudan and 59.0% in Jordan), as well as to the Reserve group (0.8% in Study III vs 0.1% in Jordan, while

this was not reported in Iran or Sudan). The data from Iran, Sudan and Jordan, unlike our study, were not limited to outpatient antibiotic dispensing data but included sales data and inpatient data [120]. This may show different proportions across the three groups. This result places Syria in one of the worst positions in terms of the quality measures of the AWaRe classification system [78].

The dispensing data in Study III included seven fixed-dose antibiotic combinations. These accounted for 29.6% of the total outpatient antibiotic dispensing. Three of these combinations were listed in the Access group. The remaining four fixed-dose combinations were not included in the AWaRe classification system and accounted for 0.8% of the total outpatient antibiotic dispensing [78]. The WHO does not recommend using these four combinations in clinical practice, as the use of fixed-dose combinations of multiple broad-spectrum antibiotics is neither evidence-based nor recommended in high-quality international guidelines [98]. Dispensing these four fixed-dose combinations presents evidence of the misuse of antibiotics in Syria [78].

We do not have a certain explanation for the regional variations in the outpatient antibiotic dispensing rates and patterns. These rates were the highest in Idlib, Quneitra and Deer el-Zour. Major parts of Idlib and Deer el-Zour were out of the Syrian government's control and were affected by the armed conflict during the study period. While the major parts of the three governorates with the lowest adjusted outpatient antibiotic dispensing rates (Al-Suwayda, Lattakia and Tartous) were under the Syrian government's control and less affected by the conflict [121]. The variations of the adjusted outpatient antibiotic dispensing rates might be related to the conflict situation in Syria [78].

The high rates of broad-spectrum antibiotics dispensing and the high percentages of the Watch group of the AWaRe classification observed in study III are concerning, as the consumption of the Watch group does significantly increase the resistance against antibiotics. The dispensing of multiple broad-spectrum fixed-dose antibiotic combinations that are neither evidence-based nor recommended in high-quality international guidelines raises questions about the adherence of the prescribers in Syria to international antibiotic prescribing guidelines. Study III provides critical findings that may help improve health insurance policies, antibiotics prescription guidelines and stewardship programs in Syria [78].

6.4. Outpatient cardiovascular diseases and diabetes medicine dispensing among the population with government health insurance in Syria (Study IV)

Study IV provided the first estimate of CVDs and diabetes medicine dispensing rates and patterns at the population level in Syria. This study used health insurance data to provide information regarding treatments for two common NCDs in Syria: CVDs and diabetes. Study IV yielded three key findings: 1) CVDs and diabetes medicine dispensing rates were low during the study period and included very low rates of insulin dispensing; 2) the dispensing rates of CVDs and diabetes medicines were lower among female beneficiaries compared to male beneficiaries; and 3) the CVDs and diabetes medicines dispensing rates were higher in governorates that were completely or mostly controlled by the Syrian government and very low to no dispensing of insulin in some governorates that were partly controlled by the Syrian government [101].

Higher rates of hypertension among middle-aged females (35 to 65 years) compared to males were reported in many countries of the Eastern Mediterranean region and North Africa, including Syria [122]. In addition, women of Arab ethnicity present with coronary artery disease 10 years earlier than those from East Asia or Europe [123]. Many factors may also contribute to the CVDs burden among women in Syria. These include religious and cultural norms and circumstances related to the lack of security in conflict zones, restricting women from sports, and limiting physical activity [123]. The low dispensing rates of CVDs medicines among females reported in study IV contrasts with other studies that have reported high rates of CVDs in females in Syria [101]. This suggests that CVDs were undertreated among females in our study population [101]. The common misperception that CVDs affect men more than women may have contributed to the suboptimal treatment of CVDs among women [124].

The dispensing rates of diabetes medicines, including insulin, were also lower among females than males; however, the WHO has reported a higher prevalence of diabetes among females than males in Syria [101, 125]. This result indicates the undertreatment of diabetes among females in Study IV [101]. Other studies have reported poorer control of type-2 diabetes among women than men [126–128]. The conflict situation in Syria may have contributed to women's vulnerability compared to men. These crises have restricted women's movement and limited their access to healthcare, including diabetic care more than men [75, 86, 101].

Study IV reported regional variation in the dispensing rates of CVDs and diabetes medicines in Syria. The Damascus countryside, Latakia, and Tartous governorates had the highest dispensing rates for CVDs and diabetes medicines [101]. The governorates of Idlib, Deer el-Zour, and Quneitra had the lowest rates of dispensing these medicines. This regional variation may be related to the conflict situation that has damaged healthcare facilities and caused unavailable healthcare services [101]. Our data did not record insulin dispensing in Idlib, Al-Hasakah, Daraa, and Deer el-Zour. The delivery of insulin in these regions may have been extremely challenging as being a cold chain product [101]. The distribution of essential medicines, including insulin, in regions affected by conflict can be complex due to political and geographical barriers, especially in the regions that are remote from the regime hubs, and are controlled by opposing forces to the Syrian government [86, 101].

6.5. Methodological considerations and factors to consider when collecting and analyzing data on use of medicines among refugees in Germany (Studies I and II)

Refugee populations are heterogeneous with regard to countries of origin, flight route and duration, exposure to different traumatic events before, during, or after the flight, and the differences in health policies that organize access to healthcare services for asylum-seekers and refugees in different host countries [129]. This heterogeneity should be considered when designing studies that focus on asylum seekers and refugees. Studies I and II focused on Syrian asylum seekers and refugees in Germany. The outcomes of these studies can not necessarily be generalized to other groups of asylum seekers and refugees from other nationalities in Germany or other countries. For example, study I focused on the barriers to accessing medicines among Syrian asylum seekers and refugees in Germany. Those granted refugee status have access to free language classes and the right to regular health insurance [21], which can reduce the impact of barriers to medicines or healthcare in general. The approval quota for staying in Germany among Syrians who have applied for asylum there is 83.7%, which is higher than for asylum seekers from Iraq (35.0%) or Afghanistan (38.0%) [130]. This means that the effect of these barriers could be higher among those groups if they were compared to Syrian asylum seekers and refugees [43].

Obtaining access to the disaggregated NRW census data of asylum seekers and refugees that could have served as a sample frame for Studies I and II was not possible. Studies that focus on asylum seekers and refugees typically lack a sampling frame, which affects the possibility of applying random sampling and reaching a representative sample of the target population [131]. Hence, nonprobability sampling methods are frequently used in studies that focus on asylum seekers and refugees. To reach a sample that can be as representative as possible, we used quota sampling in conjunction with convenience and snowball sampling. Quota sampling is accomplished by dividing a population into relevant strata [43, 132]. In Studies I and II, we divided the population according to the key demographic variables of sex and age, which helped to balance them [133]. We estimated the fraction of each stratum using census data from the statistics office of NRW, which provided aggregated data on the sex and age distribution of Syrian asylum seekers and refugees there. The sample was then defined using convenience and snowball sampling. In convenience sampling, researchers select a sample from a group of available potential cases [132]. In snowball sampling, the initially contacted respondents are asked to invite their social contacts within the population of interest to participate. Had we depended on convenience sampling only, we might not have reached groups of asylum seekers isolated from the rest of the community due to reasons such as being too sick to attend a school or a social event. Snowball sampling can help overcome this challenge and reach isolated groups [134]. To reduce selection bias that could have resulted from snowball sampling, we used multiple entry points into the Syrian asylum seeker refugee community [131, 134].

Not all participants were able to recall detailed information about the medicines they used in the past seven days. Therefore, we invited participants to bring to the interview the original packages, package inserts or patient information leaflets of all the medicines they had used in the previous seven days. The majority of interviews were conducted in the private homes of participants, in places close to their homes, or in refugee accommodation centers. This made it easier for participants to access the packages of the medicines they used in the previous seven days, or any documents related to these medicines that could help answer the survey questions accurately. Follow-up interviews to gather missing information were arranged in instances when the participants were unable to recall detailed information about the medicines they used in the past seven days, or did not bring all of the information on these medicines.

Housing status is an important social determinant of health [135]. Studies that have previously reported on health status and the utilization of healthcare services among asylum seekers and refugees in Germany were mainly based on data collected in RSACs [45, 47–49]. This could be associated with difficulties in collecting reliable data on from asylum seekers and refugees living in private housing [136]. Living in RSACs is related to higher levels of distress [137]. While other studies have provided valuable information concerning the health status or the access to healthcare services among asylum seekers and refugees who live in RSACs, their findings cannot be generalized to the majority of this population in Germany. By 2018, approximately 75% of asylum seekers and refugees in Germany lived in private housing [138]. Therefore, for this study we intentionally sought to reach asylum seekers and refugees who lived in private housing. We believe that our study sample was more representative of this population compared with other studies, which were limited to asylum seekers and refugees living in RSACs, as 78.6% of our participants lived in private housing.

6.6. Methodological considerations and factors to consider when analyzing outpatient medicine dispensing data of the population with government health insurance in Syria (Studies III and IV)

Given the many factors related to outpatient medicine dispensing data in Syria, analysis of these data poses a number of issues that must be considered. The data included in Studies III and IV were limited to people with government health insurance and did not include people living in areas of Syria that were outside of the government's control. Furthermore, the number of insured people in Idlib and Deer el-Zour was significantly lower than other governorates because large areas of these regions were beyond the control of the Syrian government.

Conducting research in a country affected by conflict is associated with numerous challenges. These include challenges related to security and safety issues, which can limit access to the study population [139], issues of ethical concern, which include asking people about traumatizing experiences, or conducting the research at a time or in a manner that could disrupt essential services delivery [140]. Through using routinely collected data in Studies III and IV, we could overcome many of these challenges. Methodological challenges can also arise from conducting research in countries affected by conflict [73]. When assessing regional variation of medicine dispensing in a country affected by conflict, it is important to take into

consideration the high mobility (displacement) of the population that results from the conflict. When assessing regional variation, studies from high-income and stable countries, such as Germany and Hungary, have calculated the number of DDDs per 1000 inhabitants of each region per day to adjust the number of DIDs according to regions or states [141, 142]. These analyses assumed that in these high-income and stable countries the inhabitants of any region or state would have access to medicines in the same region or state where they live. Patients in countries affected by conflict, such as Syria, are often forced to flee their homes to other parts of the country to access better healthcare due to the disruption of healthcare in many parts of the country [143]. Our data showed that some beneficiaries had medicines dispensed in more than one governorate. Therefore, adjusting medicine dispensing rates according to governorate by calculating the number of DDDs per 1000 beneficiaries per day for each governorate could be misleading. Hence, the medicine dispensing rates in Studies III and IV were adjusted according to governorates by calculating the number of DDED.

When comparing the medicine dispensing data from Syria with data from other countries, it is important to consider the differences in prescription regulations, reimbursement, and copayment systems between Syria and those countries. In Syria, health insurance does not cover the costs for the treatment of war injuries or injuries resulting from harmful radiation and chemical or nuclear contamination, or the treatment of psychiatric illnesses or sexually transmitted diseases [72]. This can lead to underestimating the actual use of medicines for the treatment or management of these diseases or conditions. Although not the focus of this research, it is important to note that the population with government health insurance is denied access to some essential medicines via their insurance because it excludes them in their insurance package.

7. Recommendations for policy and practice

Optimizing the access to and use of medicines to enhance the quality of healthcare for asylum seekers and refugees has global relevance. Overcoming the barriers this population faces in accessing medicines is necessary for guaranteeing their quality use of medicines. After examining the barriers to accessing medicines among Syrian asylum seekers and refugees (Study I), we recommend applying more effort to enhancing the ability of asylum seekers and refugees to learn the German language as a mid- to long-term strategy to overcome language barriers. Particular focus should be placed on female refugees, older refugees, and those with

chronic diseases or disabilities. We also recommend providing translated medical leaflets for patients who ask for them as well as providing medical interpreting services. This would help them to understand information regarding the medicines they take. Having pharmacy staff demonstrate effective cross-cultural communication skills would also be helpful in addressing barriers and any other cultural issues that could be related to the access and use of medicines. This includes the awareness about the non-acceptance of taking medicines that contain alcohol or pork products among some patients. Pharmacies staff should try to provide medicines free of alcohol or pork products to patients who refuse taking medicines containing these products [43].

By examining the rates and patterns of medicine use among Syrian asylum seekers and refugees in Germany (Study II), we found that adult asylum seekers and refugees commonly used medicines for the treatment or management of NCDs. This outcome raises the question of whether enough attention has been paid to developing policies and clinical practices to ensure NCDs care in Germany's asylum seeker and refugee population. This outcome also indicates a need to rethink the healthcare policies for asylum seeker and refugee populations during a time when the largest displacement emergency in the world has occurred in Syria, a country with a high burden of NCDs [44].

We observed high rates of outpatient antibiotic dispensing among the population with government health insurance in Syria (Study III). This included high rates of broad-spectrum antibiotic dispensing and a high percentage of the Watch group from the AWaRe classification. These results are concerning as the excessive consumption of broad-spectrum antibiotics and antibiotics from the Watch group may significantly increase antibiotic resistance. These critical findings may help improve antibiotics prescription guidelines and stewardship programs in Syria [78].

Finally, in Study IV, we presented the CVDs and diabetes medicine dispensing rates and patterns among the population with government health insurance in Syria. CVDs and diabetes medicine dispensing rates were low during the study period and included very low rates of insulin dispensing. Our study demonstrated disparities in CVDs and diabetes medicines dispensing rates in beneficiaries by sex and age. The rates of CVDs and diabetes medicines dispensing were lower among female beneficiaries compared to males. There was also significant regional variation, with low CVDs and diabetes medicines dispensing rates and low

to no insulin dispensing in some governorates that the Syrian government partly controlled. The very low rate of insulin dispensing is particular concerning as it means that those patients with diabetes type 1 would not be able to survive. Additional efforts are needed to raise awareness about the prevention and management of CVDs and diabetes especially among females in Syria and consider cultural issues that might influence access to healthcare services. Organizations that provide healthcare services in areas out of the Syrian government's control should secure the access to life-saving medicines, such as insulin.

8. Future research

The drug utilization research studies that compose the present thesis provide an overview about the access to and use of medicines among a group of Syrian asylum seekers and refugees in Germany and the population with government health insurance in Syria. The findings of these studies have meaningful implications for both policy and clinical medical practice. However, future research is required to provide further evidence that can contribute to better access to and use of medicines among both populations.

First, the data we used in the studies were limited to Syrian asylum seekers and refugees in Germany, and the population with government health insurance in Syria. Future studies should consider asylum seekers and refugees from other nationalities to provide evidence concerning interventions that can target diverse asylum seekers and refugee groups.

Second, there is also the need for data on the access to and use of medicine in different settings and population groups in Syria. This should include the availability, affordability and the quality of medicines across the country, especially in those areas that are not under the control of the Syrian government and are most affected by the conflict. These studies should in addition address the policies regulating access to essential medicines in Syria.

Third, we encourage future studies to pay more attention to the detection, treatment, and management of NCDs among forcibly displaced populations and populations living in conflict zones.

Fourth, researchers who are interested in conducting health research studies focusing on asylum seekers and refugees should not limit their data collection to those who live in RSACs or refugee camps. Instead, they should also consider recruiting participants who live in private housing in urban areas. This is particularly important given that 60% of the world's refugees

and 80% of internally displaced people shelter in cities and not in refugee camps as is often assumed [144].

Fifth, we encourage conducting qualitative research studies that could provide a better understanding of the perspectives of asylum seekers and refugees, and the populations that live in conflict zones while they access and use medicines. We encourage carefully designed longitudinal studies that include repeated qualitative interviews to better understand the experience of accessing and adhering to medicine regimens for chronic diseases among these populations. We also recommend applying mixed methods in research studies that focus on populations affected by humanitarian crisis. In study I, combining qualitative with quantitative analysis helped us to get a deeper understanding and explanation for how certain barriers affect the access to medicines among Syrian asylum seekers and refugees.

Finally, we strongly encourage the involvement of asylum seekers and refugees in health research focused on their communities. Through regular interactions with forcibly displaced populations at different stages of research projects, researchers can gain a better understanding of the perspectives and experiences of these populations. This can help overcome challenges related to conducting research among these populations and improve the research studies' quality, value, and relevance.

9. Conclusion

Drug utilization among populations affected by humanitarian crisis is understudied. This thesis studies medicines access and use among asylum and refugees and in populations living in conflict zones. These settings pose a series of challenges for researchers. This thesis illustrates how different drug utilization methods can be employed to study access to and use of medicines in these populations.

Studying access to medicines among a group of asylum seekers and refugees showed the challenges they face in accessing medicines. It identified subgroups that were more affected by these challenges, indicating the inequality in accessing medicines within the refugee and asylum seekers population we studied. This inequality could apply to the access to healthcare services in general.

Analyzing the patterns and the rates of medicine use among a group of asylum seekers and refugees in Germany reflected the healthcare needs of this group. By showing that NCDs were the most common indications that led to medicine use among adult Syrian asylum seekers and

refugees, it is time to consider NCDs in the priorities of research, healthcare practice and policies that target asylum seekers and refugees.

Using medicines dispensing data of a large sample (81,314 beneficiaries) that cover 12 months and different parts of Syria represents important methodological contributions to the published literature and provides a better understanding of medicine use in a country affected by conflict. The regional variation in dispensing medicines reflected how war impacts access to medicines. Our research showed higher rates of antibiotic dispensing, yet lower rates of CVDs and diabetes medicines dispensing in some governorates that the Syrian governorate partly controlled compared to other governorates that the Syrian government completely or mostly controlled. These outcomes can be of interest for the planning and implementing of healthcare services, including medicines supply, in conflict zones.

Based on these results, we have provided recommendation for policy and practice. These recommendations suggest short and long- and long-term intervention to overcome language barriers and address cultural challenges associated with the access to medicines. Some outcomes of the studies composed this thesis indicate a need to rethink the healthcare policies for asylum seeker and refugee populations and pay additional attention to NCDs and raise awareness about the prevention and management of CVDs and diabetes among populations affected by humanitarian crisis, especially among females in a country that is affected by conflict, such as Syria.

Annex 1: The papers included in this dissertation

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12. Appendix



Article

Barriers to Accessing Medicines among Syrian Asylum Seekers and Refugees in a German Federal State

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Abstract: In Germany, asylum seekers and refugees (AS&Rs) face challenges when accessing health-care services including medicines. The aim of this study was to explore the barriers to accessing medicines among Syrian AS&Rs in the state of North Rhine-Westphalia, and to provide an understanding of their perspectives towards taking medicines that contain alcohol or pork products. This study is based on a cross-sectional survey using a combination of sampling methods. We used descriptive statistics to analyze quantitative data. Participants' answers to an open-ended question yielded qualitative data that were categorized based on the thematic areas they discussed or addressed. Among the 1641 respondents, language barriers had more of an effect on the access to medicines than any other factor studied. The effect of language barriers on access to medicines was more pronounced for female participants, those who were older than 50 years, and participants who had chronic diseases in comparison to the other groups of participants. Male participants and those younger than 50 years of age showed more acceptance towards taking medicines that contain alcohol or pork products. Based on our results, we recommend providing more support for AS&Rs to learn the German language, particularly for female refugees, older refugees, and those with chronic diseases or disabilities. We also recommend providing translated medical leaflets for patients who wish to receive them in their native language. Healthcare providers should try to consider the special conditions of AS&Rs patients and take into account their perspectives about treatments and diseases.

Keywords: asylum seekers and refugees; Syria; Germany; North Rhine-Westphalia; access; barriers; language; medicine; acceptance; alcohol; pork products



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1. Introduction

War, conflict, human rights violations, and disasters worldwide forced 79.5 million people to flee their homes by the end of 2019. This is the highest number ever recorded for displaced populations. Globally, Syrians form the largest group of refugees (6.7 million). While the majority of refugees (83%) live in countries that are neighbors to their countries of origin, smaller numbers can reach Europe [1]. Germany hosts the largest group of refugees in Europe (1.5 million refugees in total), with Syrian asylum seekers and refugees (AS&Rs) constituting the largest group of the total AS&Rs population in Germany (42%) [1,2]. This number is low considering the global trend of forced migration or in comparison to the number of hosted refugees in countries such as Turkey (3.6 million). However, since the peak of migration in 2015, the term 'refugee crisis' has frequently been in the public discourse, and the issue of migration has become an essential part of political debates both in Germany and other European countries [3,4].

An asylum seeker is: "an individual who is seeking international protection and whose claim has not yet been finally decided on by the country in which the claim is submitted" [5]. A refugee, according to the Geneva 1951 refugee convention, is: "someone who is unable or unwilling to return to their country of origin owing to a well-founded fear

of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion" [6].

The rapid increase in the number of refugees arriving in Germany has posed challenges to public health authorities who provide for the health needs of this group [7]. Access to healthcare services among asylum seekers in Germany is restricted. Articles 4 and 6 of the asylum seekers benefit act (*Asylbewerberleistungsgesetz, AsylbLG*) of 1993 state that asylum seekers are entitled to emergency medical care, treatment for acute and painful conditions, care during pregnancy and childbirth, vaccinations and other "necessary preventive measures". Asylum seekers are also entitled to additional care in cases that could be evaluated or approved to be "essential" for the preservation of health [8]. Once asylum seekers receive a refugee status, they can obtain regular access to health care through normal statutory health insurance. Since March 2015, asylum seekers have been able to regularly access healthcare services after waiting 15 months rather than 48 months [8]. However, even after this improvement in the asylum-seekers benefit act, the restriction to healthcare has been described as *untenable* [9]. Bozorgmehr et al. has argued that restricting the healthcare access of any population group based on their residency status can be regarded as a violation of the right to health [10].

In Germany, there is a co-payment for prescription medicines. Statutory insured persons pay ten percent of the sales price per package for each prescription medicine, up to a maximum of ten euros (about USD12) and a minimum of five euros (about USD6). Children under the age of 18 are exempt from all co-payments. Over-the-counter (OTC) medicines are usually not reimbursed by statutory health insurance. However, this does not apply to children under the age of twelve and adolescents, up to the age of 18, with developmental disorders. For these groups, OTC medicine prescribed by a doctor will be reimbursed [11]. These regulations also apply to refugees and asylum seekers who stay in Germany for more than 15 months. Asylum seekers who stay in Germany for less than 15 months are exempt from co-payments for medicines. However, these medicines need to be prescribed for acute and painful conditions, or for the recovery of illnesses [12]. In 2016, Germany spent more on medicines on a per capita basis (EUR 572) compared to other European Union member states [13]. Expenditures for medicines among asylum seekers in Germany in 2016 were approximately half of what spent on a matched group of statutory insured people [14].

The legal restrictions to accessing healthcare among asylum seekers are also coupled with administrative barriers in some parts of Germany [8]. Before 2014, asylum seekers received quarterly renewable healthcare vouchers, which could be used for doctor's visits. However, they needed to make a personal request at a social welfare office to obtain these vouchers [15]. This procedure has been criticized, as social-welfare-office employees do not typically have the medical qualifications to make decisions regarding the need for medical treatment [16]. Starting from 2015, each federal state of Germany was able to decide whether to keep the healthcare vouchers for asylum seekers or grant them electronic health insurance cards from the beginning of their stay. The majority of German federal states decided to introduce electronic health insurance cards, with the exception of the states of Saxony, Bavaria, and some municipalities in North Rhine-Westphalia (NRW) [15,17,18].

In addition to the system-related restrictions or administrative barriers, AS&Rs face other obstacles when accessing healthcare services. These include language barriers, personal and cultural beliefs, and financial costs [18–20], all of which can have an effect on the consumption of medicines [21]. Barriers in accessing medicines can affect patient safety [19] and limit adherence to treatment regimens [22]. Therefore, overcoming these barriers is necessary to improve the quality of access to medicines and to ensure that patients obtain the right choice of medicine at the right time [19]. Cultural and religious beliefs can also have an effect on access to healthcare and treatment [23]. According to the Federal Office for Migration and Refugees (BAMF), approximately 84% of Syrian nationals who applied for asylum in 2019 mentioned Islam as their religion [2]. Islam recommends avoiding the consumption of food or beverages that contain alcohol or pork products [24],

both of which maybe present as active ingredients in medicines, e.g., porcine heparin, as excipients, ethanol in many pharmaceuticals, and pork gelatin in capsules [25].

This research is part of a larger study investigating the access to, and use of, medicines among Syrian AS&Rs in the German state of NRW, which has the largest population in Germany and the highest number of registered AS&Rs [2]. The aim of this study was to explore the barriers to accessing medicines among Syrian AS&Rs, and to provide an understanding of their perspectives towards taking medicines that contain alcohol or pork products.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional study using a survey for data collection. We used descriptive statistics to analyze quantitative data. Responses to open-ended survey questions were studies using thematic analysis. The qualitative data analysis supported the interpretation of the quantitative findings.

2.2. Sampling Design

Studies that focus on AS&Rs typically lack a sampling frame, which affects the possibility of using random sampling and obtaining a representative sample [26]. Hence, nonprobability sampling methods are typically used [27]. To reach a sample that can be as representative as possible, we used quota sampling in conjunction with convenience and snowball sampling. Quota sampling is accomplished by dividing a population into relevant strata [27]. In this study, we divided the population according to the key demographic variables, age and sex, which helped to balance them [28]. We estimated the fraction of each strata using the census from the statistics office of NRW, which provided information about the age and sex distribution of Syrian AS&Rs in NRW [29]. The sample was then defined using convenience and snowball sampling. In convenience sampling, researchers take a sample from a group of available, potential cases [27]. In snowball sampling, the respondents who are initially contacted are then asked to invite their social contacts within the population of interest to participate. Had we depended on convenience sampling only, we might not have reached groups of asylum seekers isolated from the rest of the community due to reasons such as being too sick to attend a school or a social event. Snowball sampling can help in overcoming this challenge and reaching isolated groups [30]. To reduce selection bias that could have resulted from snowball sampling, we used multiple entry points into the Syrian refugee community [26,30]. To ensure that our sample distribution is similar to the target population distribution along the key demographic variables, age and sex, we stopped interviewing AS&Rs who would belong to a certain strata once the pre-estimated fraction of this strata has been met. Since adequate data that report the use of medicines among refugees in Germany were not available, we were unable to perform a power calculation to determine the sample size for this study. We aimed for a relatively large sample size (1500 individuals). This was a pragmatic decision based on discussions with a biostatistician.

2.3. Participants and Eligibility Criteria

Inclusion Criteria

AS&Rs of all ages who had their addresses registered in the state of NRW were eligible. Syrians, including stateless Palestinian Syrians and Syrian Kurds, were also eligible. In this study, the term refugee included those whose asylum applications in Germany had been approved by the BAMF, those who were entitled to refugee status or subsidiary protection, and those who were allowed to stay in Germany due to a ban on deportation.

2.4. Community Involvement

Conducting research in refugee populations is challenging as the population is difficult to reach and sample for a variety of reasons such as inadequate sampling frames,

language or cultural issues, concerns about privacy, or fear due to experiences in home countries [31,32]. To address the challenges of participant recruitment and to enhance our understanding of the study matter, we enlisted the help of Syrian activists and other prominent members of the Syrian community in NRW who voluntarily took part in different stages of our research, including during the development of our questionnaire. They provided comments and suggestions for the questions we included and on its translation. We also asked Syrian AS&Rs to suggest places and locations where we could recruit participants for the study. In addition, many AS&Rs played the role of access points in our snowball sampling and motivated other potential participants to take part in the study. Finally, Syrian AS&Rs were asked to comment and provide feedback on the study's findings.

2.5. Questionnaire Development

The questionnaire we used was primarily based on validated instruments and questions that have been applied in other studies. Information about the use of medicines was collected using questionnaires from the German Health Interview and Examination Survey for Adults (DEGS) [33], and the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [34]. Our questionnaire also included the Brief Medication Questionnaire (BMQ) [35].

Our questionnaire contained items that also asked about the barriers facing AS&Rs when accessing medicines, which was developed for this study. This part of the questionnaire was based on information from previous studies that focused on barriers to accessing healthcare services or medicines among refugees or migrants in different countries [19,20,22]. When designing this part of the questionnaire, we took into consideration the perspectives of Syrian AS&Rs. Participants suggested adding the factor 'unavailability of certain medicines in German pharmacies', as they mentioned that certain medicines used in Syria, or specific doses of medicines, were not available in Germany. Participants also suggested adding the possibility of purchasing medicines over the counter as another factor, as it is common to purchase some medicines (such as antibiotics) without a prescription in Syria [36], which is not possible in many European countries [37]. Both suggestions were included in our questionnaire.

Items in this part of the questionnaire were categorized into two sections. One included questions about the impact of four factors on accessing medicines: (*Based on your experience, how much do these factors limit your access to medicine in Germany?*): (1) language barriers, (2) availability of certain medicines in German pharmacies (*Finding the medicine I need in the pharmacies*), (3) financial barriers (*I need to pay for the medicine*) and, (4) possibility of purchasing the medicines without a prescription (*The medicine I need is a prescription medicine*). Participants were asked to give their answers to each of these items on a scale from 1 to 7 (1 = No effect at all, 7 = Very large effect). The second group of questions focused on acceptance levels in regard to taking any medicine that contained alcohol or pork products. Supplementary File 1 includes the questions from this part of the questionnaire.

The remaining parts of the questionnaire included questions regarding sociodemographic and socioeconomic parameters taken from the validated instruments of different studies as well as an open-ended question that solicited comments. [38–40]. The questionnaire was available in three versions: one for adults (≥ 18), one for children (0–13) whose parents answered for them, and a version for adolescents (14–17 years old) who answered the questions themselves after the approval of one of their parents or guardians. Supplementary Table S1 provides an overview of the questionnaire.

To ensure that the questions would be culturally appropriate for our target population, we discussed the questionnaire with five Syrian refugees. We also contacted nine researchers and practitioners with work experience in the field of refugee healthcare and/or drug utilization research and asked them to check for face and content validity.

The questionnaire was developed in English. Some of the included questions underwent a validated translation to Arabic. To obtain a comprehensive Arabic version of

the questionnaire we carried out the following recommended activities [41]: (1) forward translation: one of the researchers (SA), whose mother tongue is Arabic and who speaks fluent English; (2) expert panel: a panel of five experts, all of whom are native Arabic speakers and fluent in English, discussed the translated version of the questionnaire. A back translation was not possible due to limited time and resources; and (3) cognitive pre-test: we asked twelve AS&Rs to answer our questionnaire. Respondents were asked about any term or question they found unclear or possibly offensive.

In a pilot study, the questionnaire was tested in 70 participants (50 adults, 9 adolescents, and the parents of 11 children). After running the pilot study, we realized that reaching or contacting female and older participants (≤ 60 years of age) demanded more effort. In addition, some changes to the questionnaire were made, e.g., we changed the order of some questions so they were easier to answer. Supplementary Table S1 lists these changes.

2.6. Recruitment and Data Collection

One researcher (SA), who is fluent in Arabic and with a trusted relationship with the community, recruited participants for the study. The investigator visited fifteen refugee accommodation centers in the larger Cologne area. The investigator visited the accommodation centers more than once to meet the highest possible number of potential study participants. In addition to accommodation centers, the investigator visited a community center that ran a language school and consultation office for refugees three times per week, on average, during the data collection period. We recruited for this study in other places frequented by the Syrian community, including Syrian restaurants and cafes, social events for the Syrian community and at exhibitions about Syria.

The investigator introduced himself to the participants in Arabic, informed them of the study, and explained that participation was voluntary, and that the questionnaire would not include any questions that could lead to personal identification. Data collection in this study was based on: (1) investigator-administered personal interviews about medicines use and (2) self-filled questions about demographics. We administrated a digital form of the questionnaire on tablet computers using the survey tool Qualtrics [42]. Data for this study was collected between 10 July 2019 and 31 December 2019.

2.7. Data Analysis

Two types of data were collected: (1) qualitative data from the answers to the open-ended question regarding access to and the use of medicines in Germany and, (2) quantitative data from the answers to the remaining questions.

2.7.1. Qualitative Data Analysis

After translating the answers to the open-ended question into English, we used thematic analysis to categorize these answers in an Excel sheet (Microsoft office 2019) based on the following thematic areas that were discussed or addressed by the participants: language barriers, unavailability of certain medicines in pharmacies, financial barriers, purchasing medicines without a prescription, and acceptance of taking medicines that contain alcohol or pork products. The thematic analysis was done by the first two authors (SA, VJW). Predefined and newly emerging codes were used to categorize the data. For instance, predefined codes included pork, alcohol, and faith. Newly emerging codes were stigma and the role of family members to overcome language barriers. Triangulation between the thematic analysis and the quantitative findings were used to enhance our understanding of the nature and relevance of the access barriers described. Significant sections from participant statements were selected to be included in the results section. In addition, the Patients' Lived Experience with Medicine model (PLEM) [43] was used to describe and summarize the aspects of participants in regard to accessing and using medicines. The PLEM module has three major themes: medicines-related burdens, medication-related beliefs, and medication-taking practice [43].

2.7.2. Quantitative Data Analysis

We calculated the medians and interquartile ranges (IQRs) for the questions on barriers to medicines among adult participants and parents. To detect significant differences for each item, we conducted nonparametric analyses, as our data showed some evidence of a skewed distribution. We used the Mann–Whitney U test to examine the differences between female and male adult participants, and between participants with and without chronic diseases based on their answers to the questions regarding barriers to accessing medicines. We used the Kruskal–Wallis test to investigate differences between age groups.

We calculated the medians and IQRs for ordinal measurement items concerning the acceptance of taking a medicine that contained alcohol or pork products. The same nonparametric analyses were applied to detect significant sex and age differences, or differences between participants with and without chronic diseases for each of those questions. A *p*-value of 0.05 was used as a cut-off value for significance in all of the tests. Analyses of quantitative data were conducted using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA).

3. Results

We recruited 1,641 Syrian AS&Rs. Of these, 1063 were adults (≥ 18 years), 456 were children (≤ 13 years) for whom one parent answered the questions for them, and 122 were adolescents (14–17 years). Males comprised 62.4% of the participants. Table 1 lists the sociodemographic characteristics of the participants.

Table 1. Sociodemographic characteristics of the study participants.

Participant Characteristics	Number of Participants	Proportion (%)
Sex		
Male	1024	62.4%
Female	617	37.6%
Age		
0–17	578	35.22%
18–29	468	28.52%
30–39	318	19.38%
40–49	158	9.63%
50–59	78	4.75%
60≤	41	2.5%
Health insurance		
Yes	1616	98.48%
No	23	1.4%
Missing	2	0.12%
Residency status		
Refugee status or subsidiary protection	1603	97.68%
Asylum seeker	38	2.32%
Accommodation		
Initial reception center	18	1.1%
Long-term accommodation center	318	19.38%
Private housing	1289	78.55%
Missing	16	0.97%
Chronic disease (Adults only)		
Yes (22 different chronic diseases)	146	13.74%
No	914	85.98%
Missing	3	0.28%
The most common chronic diseases		
Hypertension	71	6.68
Diabetes	44	4.14
Hypothyroidism	30	2.82
Hyperlipoproteinemia	21	1.98
Anemia	21	1.98
Other chronic diseases	66	6.21

Table 1. Cont.

Participant Characteristics	Number of Participants	Proportion (%)
Employment (Adults only)		
Employed	249	23.42%
Retired	16	1.51%
Vocational training	237	22.29%
Not employed	537	50.52%
Missing	24	2.26%
German language level ¹		
A1-A1	242	22.77%
B1-B2	495	46.57%
C1-C2	168	15.8%
None	131	12.32%
Missing	27	2.54%
Marriage status (Adults only)		
Single	381	35.84%
Married	613	57.67%
In a relationship	27	2.54%
Divorced	19	1.79%
Widowed	13	1.22%
Missing	10	0.94%

¹ Language levels were classified according to the Common European Framework of Reference for Languages (CEFR) [44].

Approximately 41% of adult participants took at least one medicine in the last seven days before the data collection. The prevalence of taking at least one medicine increased with age (Figure 1)

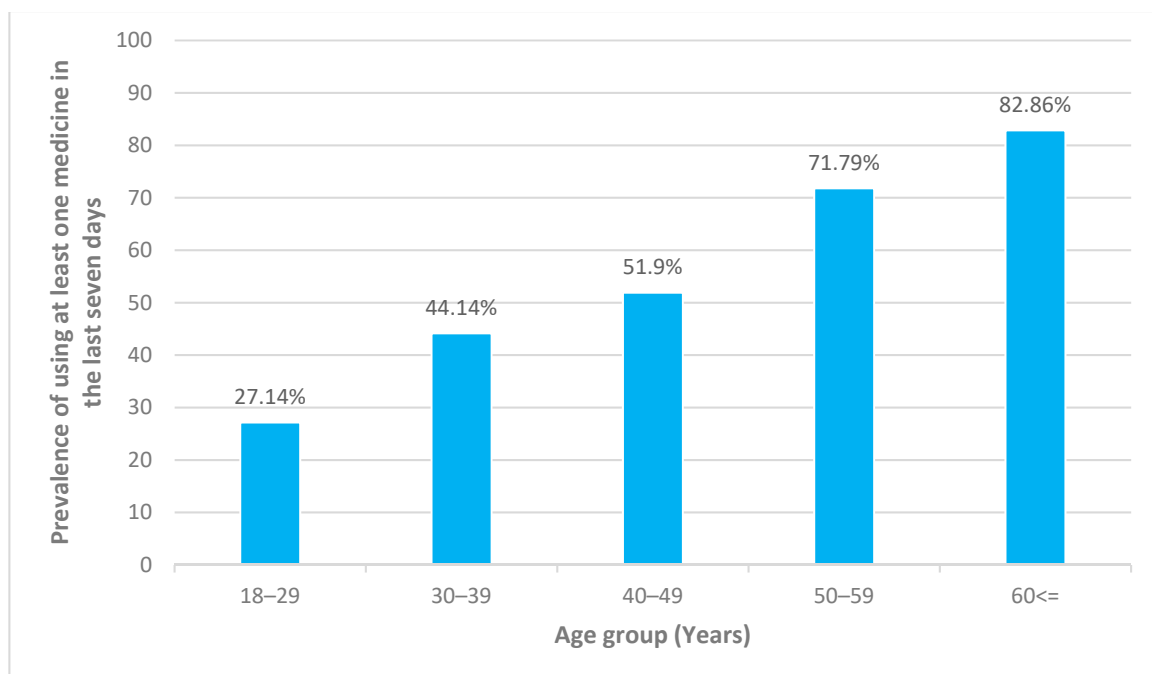


Figure 1. Prevalence of using at least one medicine in the last seven days among adult participants in each age group.

3.1. Barriers to Accessing Medicines

Among the adult and parental respondents, language barriers had the strongest effect on accessing medicines (median 3 (2–5)), which was followed by barriers related to purchasing a medicine without a prescription (median 1 (1–3)). Financial barriers and the unavailability of certain medicines in German pharmacies had the lowest effect

on the adult participants (median 1(0)) (Table 2). There was a statistically significant difference ($p < 0.001$) between adults and parental respondents concerning the effect of language barriers on access to medicines. Language barriers had a stronger impact on parents attempting to access medicines for their children in comparison to adults wanting access for themselves (Table 2). There was no statistically significant difference ($p > 0.05$) between adults and parental participants regarding the effect of the other factors that might form barriers.

Table 2. Descriptive statistics for different participant groups according to four factors influencing access to medicines.

Participant Subgroups			Language Barriers	Unavailability of Certain Medicines in Pharmacies	Financial Barriers	Purchasing Medicines without a Prescription
Total ¹						
Adults	Median (IQR) ²		3 (2–5) ***	1 (0)	1 (0)	1 (1–3)
Parents	Median (IQR)		4 (3–5) ***	1 (0)	1 (0)	1 (1–3)
Adults Sex ¹						
Female	Median (IQR)		4 (2–5) ***	1 (0)	1 (0)	1 (1–3)
Male	Median (IQR)		3 (2–4) ***	1 (0)	1 (0)	1 (1–3)
Age ³						
18–29	Median (IQR)		2 (2–4) ***	1 (0)	1 (0) **	1 (0) *
30–39	Median (IQR)		4 (2–5) ***	1 (0)	1 (0) **	1 (1–3) *
40–49	Median (IQR)		4 (3–5) ***	1 (0)	1 (0) **	1 (1–3) *
50–59	Median (IQR)		5 (4–6) ***	1 (0)	1 (0) **	1 (1–3) *
≤60	Median (IQR)		5 (4–6) ***	1 (0)	1 (1–3) **	1 (1–4) *
Chronic diseases ¹						
Yes	Median (IQR)		4 (3–5) ***	1 (0)	1 (1–2) ***	1 (1–3) ***
No	Median (IQR)		3 (2–5) ***	1 (0)	1 (0) ***	1 (1–2) ***

¹ Mann–Whitney U test. ² Interquartile range. ³ Kruskal–Wallis ANOVA Test. * Difference is significant at the 0.05 level. ** Difference is significant at the 0.01 level. *** Difference is significant at the 0.001 level.

There was a statistically significant difference ($p < 0.001$) between adult males and females in regard to the language barriers, with a stronger effect observed in females (Figure 2). There were no statistically significant differences ($p > 0.05$) between males and females regarding the other three factors (Table 2).

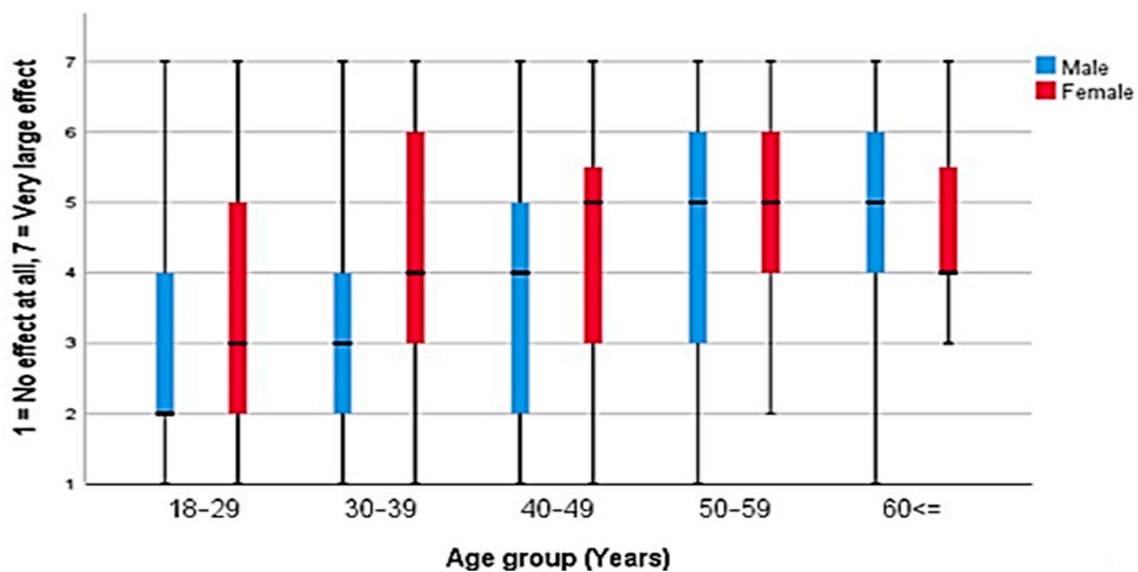


Figure 2. The effect of language barriers among adult participants according to sex and age.

A significant difference ($p < 0.05$) between the different adult age groups was found in relation to access to medicines and language barriers (Figure 2), financial barriers, and purchasing medicines without prescriptions (Table 2). The effects of these three factors were stronger in those older than 50 years of age. There was no statistically significant

difference ($p > 0.05$) between the different age groups concerning the unavailability of certain medicines in German pharmacies (Table 2).

There was a significant difference ($p < 0.001$) between participants with and without chronic diseases on the effect of language barriers, financial barriers, and purchasing medicines without prescription on access to medicines, with the effects of these three factors stronger in those with chronic illnesses. However, there was no statistically significant difference ($p > 0.05$) between the two groups according to the unavailability of certain medicines in German pharmacies (Table 2).

Ninety-seven participants provided answers to the open-ended question regarding their experiences accessing and using medicines. Many of the participants stated that they had experienced no health problems since their arrival and, therefore, had never been to a doctor or a pharmacy in Germany. Hence, they were not confronted with any barriers to healthcare services in general. One participant who had multiple morbidities and took numerous medicines explained that he did not know, due to language barriers, the order in which he needed to take his medicines. Some of the participants with chronic diseases or disabilities mentioned that their health issues had reduced their ability to learn German. For example, for health reasons, they could not visit German language classes: "I started to learn the language, but I couldn't follow because I could see only up to 15%. In the school they told me that I should go to a school for disabled people."

Some participants explained how they overcame language barriers by having family members accompany them to doctors or pharmacies: "Sometimes when I go to the doctor, my daughter comes with me to translate for me." One participant suggested pharmacists hand out an Arabic version of the medicines leaflets to help overcome the language barrier.

Apart from language barriers, two participants mentioned barriers encountered when purchasing medicines without a prescription. In both cases, the participants referenced the effort needed to get an antibiotic in Germany due to the regulations regarding dispensing medicine. Two participants cited financial barriers by mentioning that medicines are expensive in Germany, especially those that are not covered by health insurance.

Many participants mentioned that their perspectives on the treatment and management of their diseases were not taken in account by physicians, due to language barriers. Some of them were not offered any treatments for what they described as serious pain or health problems and were, instead, advised to drink water. One participant described a medical error that involved administering a medicine that caused her harm. These issues can be directly linked to language barriers. The qualitative data included also comments from participants about medications adverse events and medication routines. Some participants stated that positive beliefs and experiences with medicines were a main driver for them to adhere to medicines.

3.2. Acceptance of Medicines Containing Alcohol or Pork Products

Among adult participants, half of the observations concerning the acceptance of taking medicines that contain alcohol or pork products (on a scale of 1–7) were above the median value 4 (1–7). There was a statistically significant difference ($p < 0.001$) between male and female adult participants in regard to taking medicines that contain alcohol or pork products. Male participants displayed more acceptance than females (Table 3). There was a significant difference ($p < 0.001$) between the age groups as well, with those younger than 50 years old more accepting of the idea than older participants. (Table 3).

There was no statistically significant difference between participants with and without chronic diseases in terms of their acceptance towards taking medicines that contain alcohol or pork products. However, there was a statistically significant difference ($p < 0.001$) between participants with and without chronic diseases regarding their acceptance of medicines that contain alcohol or products that do not have other alternatives. In this case, participants with chronic diseases showed more acceptance of medicines that contain alcohol or pork products (Figure 3). We also observed that some participant subgroups

showed more acceptance towards taking a medicine with alcohol than with pork products (Table 3).

Table 3. Descriptive statistics for different participant subgroups concerning their acceptance of taking medicines that contain alcohol or pork products.

Participant Subgroups			Alcohol	Pork Products
Total				
Sex ²	Adults	Median (IQR) ¹	4 (1–7)	4 (1–7)
	Female	Median (IQR)	1 (1–4) ***	1 (1–4) ***
Age ³	Male	Median (IQR)	7 (3–7) ***	4 (2–7) ***
	18–19	Median (IQR)	7 (1–7) ***	7 (1–7) ***
	30–39	Median (IQR)	4 (1–7) ***	4 (1–7) ***
	40–49	Median (IQR)	4 (1–7) ***	3 (1–7) ***
	50–59	Median (IQR)	4 (1–7) ***	4 (1–7) ***
	≥60	Median (IQR)	4 (1–5) ***	4 (1–4) ***
Chronic diseases ²	Yes	Median (IQR)	4 (2–7)	4 (1–7)
	No	Median (IQR)	4 (1–7)	4 (1–4)

¹ Interquartile range. ² Mann–Whitney U test. ³ Kruskal–Wallis ANOVA Test. *** Difference is significant at the 0.001 level.

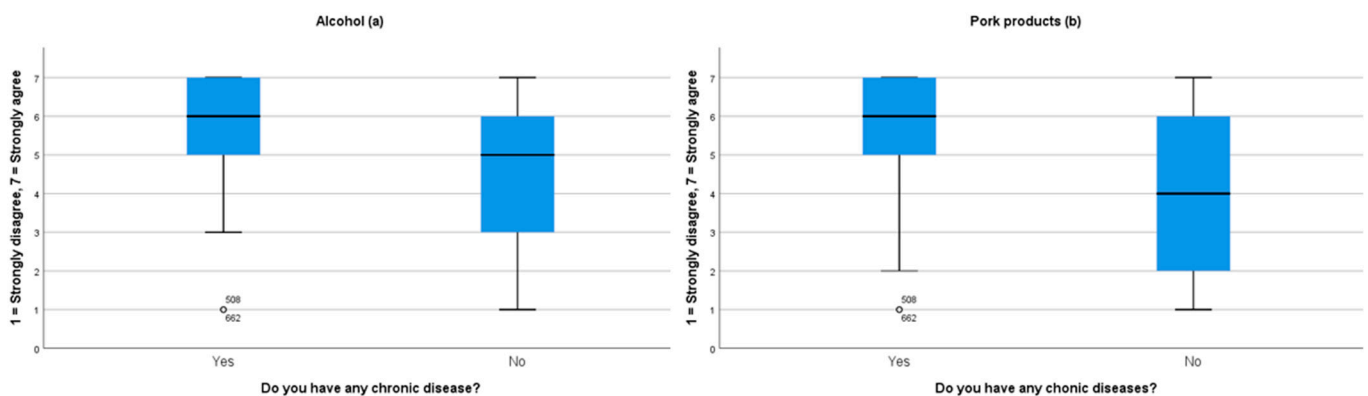


Figure 3. This figure represents the respondents’ answers to whether they would be willing take medication containing (a) alcohol or (b) pork products in cases when there are no other alternatives to these medicines.

An analysis of the qualitative data provided explanations for some of the perspectives concerning the acceptance of taking medicines that contain alcohol or pork products. Many of the participants suggested that they would take these medicines if there was no other alternative, as it would be for medical reasons: “If a medicine has no alternative that is free of alcohol or pork products, I would take it then. God did not ask us to do the impossible.” Other participants explained why they would not think to check whether a medicine contained these products. They suggested that it was difficult to check the ingredients of medicines due to language barriers, and that it did not occur to them that medicines would contain these products, as they are not used to this in Syria.

4. Discussion

To the best of our knowledge, this is the first study to investigate and report on the barriers encountered when accessing medicines among a group of AS&Rs in Germany. Our results fill important knowledge gaps and support the development of recommendations to improve access to medicines for AS&Rs. We found that language barriers formed the major obstacle compared to the other three barriers we considered. Other studies have also reported that language barriers usually affect access to medicines among different groups of

refugees in different countries [19,20,45]. For example, in a study from England, researchers found that refugee parents considered language barriers to be a major factor that limited their access to medicines for their children [46]. Language barriers were followed by barriers related to obtaining medicines without a prescription, financial barriers, and the unavailability of certain medicines in German pharmacies. The qualitative data illustrated the challenge related to obtaining medicines without a prescription by highlighting the difficulty in obtaining certain medicines, such as antibiotics, without a prescription in Germany. It is simple to get these medicines without a prescription in Syria [37]. Financial barriers and the unavailability of certain medicines in German pharmacies both played minor roles in limiting access. This can be explained by the fact that 98% of the participants were covered by regular health insurance. It is noteworthy, that this is not the financial burden for the individuals because the health system is financing medicines. Germany has a high level of public spending on health. Out-of-pocket expenditure on health is only 12% in Germany. As the results of this study show, financial burden was not found to be a relevant barrier. This is very different from many other countries in which medicines is entirely or almost entirely financed by individuals [47]. A study that focused on barriers to accessing healthcare services among refugees in Austria also reported minor effects due to financial barriers [48].

Our results showed a statistically significant difference between females and males concerning the effect of language barriers on access to medicines, with the effect being stronger and more limiting for females. In Germany, female refugees attend integration courses less frequently and with longer delays after their arrival in Germany in comparison to males. Female refugees also assessed their German language skills as weaker than males do. This may be due to female refugees having less opportunities for using or practicing the German language. Female refugees who come to Germany with families tend to focus on housing provision and childcare and would, therefore, have less time to learn German [49]. This is not a new phenomenon. Studies on refugees who arrived in Germany in the nineties also showed a slower integration of female refugees compared to their male counterparts [49,50].

There was a statistically significant difference between participants from different age groups according to the effects of language barriers, financial barriers, and the possibility of purchasing a medicine without a prescription. The impact of these three factors on limiting access to medicines was strongest among participants who were older than 50 years of age. Older age is associated with a higher risk of chronic diseases and higher medical referral rates [20]. One study has shown that older refugees had lower levels of education, higher unemployment rates, and poorer language skills of the hosting countries in comparison to younger refugees [51]. This could explain why the effect of these factors was strongest among older participants. Our qualitative analysis also demonstrated that some young respondents, due to their good general health status, seldom acquired any medicines after their arrival to Germany. Hence, they were rarely confronted with the process of trying to get prescription medicine.

There was also a statistically significant difference between those with and without chronic diseases according to language barriers, financial barriers, and the possibility of purchasing medicines without a prescription. Our qualitative data analysis indicated that some participants with chronic diseases or disabilities faced reduced opportunities for learning German due to their health issues. Treating chronic diseases usually requires the long-term use of medicines [23]. Many of these medicines can only be purchased with a prescription and would require co-payments from the patients. This may be why access to medicines in this group was more strongly influenced by language barriers, financial barriers, and the possibility of purchasing a medicine without a prescription.

Ninety-seven participants provided comments about their perspectives or experiences related to medicines access and use in Germany. The answers to the open-ended question did not represent the total sample but they provided an overview of the experiences or perspectives of these ninety-seven participants regarding medicines access and use. Why

many participants did not provide an answer to this question, is unclear but it is likely that they did not have comments regarding medicines access and use. Our qualitative analysis illustrated some of the strategies participants have used to overcome language barriers. For example, some mentioned that family members would accompany them to doctor appointments to translate for them. While this might be a practical solution, there is an important ethical issue associated with using an untrained person to interpret health information, and with exposing a family member, especially children, to information regarding traumatic experiences [22]. One participant suggested preparing medicine leaflets in Arabic. This could be an effective and feasible solution that could help many individuals overcome some of the language barriers they encounter, as the Arabic literacy rate among Syrian nationals is high (86.4%) [52].

The qualitative data also included comments from participants about how their perspectives about their health conditions were not taken into account by healthcare professionals. This led to ineffective treatment for their health conditions. According to the World Health Organization's report, Medication Without Harm patients are generally "passive recipients" of medicines and are often not involved in the process of the treatment or management of their diseases [53]. However, taking into consideration patient perspectives are major contributors to a successful treatment [54]. Refugees might be more prone to being left out of the treatment decision-making process due to language barriers. A participant mentioned that she, due to a medical error, applied a medicine that caused her harm. Medicines sometimes have complex names or packaging, and may lack sufficient or clear information. Confusing medicines names, labeling, and packaging are frequent sources of error [53]. AS&Rs can also be more prone to these errors due to language barriers. Providing a translated version of a medicine's leaflet to patients who ask for it could be helpful in reducing the possibility of medical errors. More research is needed to identify the demand and need for information on medicines, their risks (e.g., antimicrobial resistance) and benefits in this population.

While developing the questionnaire for our study, Syrian AS&Rs suggested adding the challenge of purchasing a medicine without a prescription as a barrier to accessing medicines. Participants in this study considered purchasing medicines without a prescription as the second most important factor to limit access to medicines after language barriers. Restricting the dispensing of antibiotics to prescription-only is recommended to promote the adequate use of medicines and prevent increases in antimicrobial resistance [37].

There is a lack of information concerning refugees' acceptance of 'Western medicine' [22]. In our study, we presented the perspectives of a group of adult Syrian AS&Rs on their acceptance towards taking medicines that contain alcohol or pork products. Accepting the idea of taking these medicines is an issue, not only for Muslim patients, but also for those of other religions such as Jews, or those who follow certain diets (vegans) [25].

We found a significant difference between female and male participants regarding their acceptance towards taking medicines that contain alcohol or pork products, with females being less accepting than males. There was also a significant difference between age groups. Those who were younger than 50 years of age showed more acceptance than those who were older. We do not have an explanation for these results and suggest further qualitative studies are needed to understand them.

There was no statistically significant difference between those with and without chronic diseases in terms of their acceptance towards taking medicines that contain alcohol or pork products. However, those with chronic diseases were significantly more accepting of these medicines in instances where there was no other alternative to the medicines. Our qualitative analysis illustrated the opinions of some participants and showed that if there were no alternatives, then taking these medicines should be tolerated. One study has suggested that Muslims can take medicines that contain alcohol or pork products if there is no alternative and in cases of emergency [55].

Our participants showed more acceptance towards taking medicines that contain alcohol than ones that contain pork products. Some Muslim countries accept or allow the

use of medicines that contain alcohol (benzyl alcohol, methyl alcohol, and polyethylene alcohol) [56]. However, this does not apply to those that contain pork products. Some schools of Islamic jurisprudence refuse to accept the use of medicines that contain pig gelatin even though it is highly purified and so degraded that the pig DNA cannot be detected, nor can the original source of the gelatin be identified [57].

The results of this study help to understand the barriers to accessing medicines among Syrian AS&Rs not only in NRW, but in other parts of Germany as well. Barriers to accessing medicines among Syrian AS&Rs might have been different, or had different effects, if we had compared them to other groups of refugees from different nationalities. Those who are granted a refugee status have access to free language classes and the right to regular health insurance [12], which can reduce the impact of barriers to medicines or healthcare in general. The approval quota for staying in Germany among Syrians who have applied for asylum in Germany is 83.7%, which is higher than for asylum seekers from Iraq (35%) or Afghanistan (38%) [2]. This means that the impact of these barriers could be higher among those groups if they were to be compared to Syrian AS&Rs.

Strengths and Limitations

Finally, a number of important limitations need to be considered. Due to the lack of a sample frame, we used non-probability sampling methods. This can affect the possibility of the representativeness of our results to the Syrian AS&Rs population in NRW or in greater Germany. Nevertheless, given that there is no data available that would allow for drawing a representative sample, this is an important first step towards understanding medicine access barriers among Syrian AS&Rs in Germany. To enhance the likelihood of our sample being representative, we used a combination of sampling methods and recruited study participants from a wide range of settings that are typical to our study population. We also aimed for, and achieved, a large sample size that included a diverse group of AS&Rs. Another strength of our study is that we involved our target population in several stages of the research. This was helpful in ensuring that our investigation was well-adapted to the culture of the target population. The qualitative analysis complemented the quantitative analysis and provided a deeper understanding and explanation for how certain barriers affect Syrian asylum seekers and refugees' access to medicine, and their acceptance towards taking medicines that contain alcohol or pork products. However, there are still many knowledge gaps about medicines access in AS&R in Germany. For instance, more qualitative research is needed to provide a better understanding for AS&Rs perspectives towards accessing and using medicines. To study medicines use among specific age groups of AS&Rs, future studies should consider larger sample sizes.

5. Conclusions

Optimizing the access to and use of medicines to enhance the quality of health care for refugees has global relevance. Overcoming the barriers facing refugees in accessing medicines is necessary for guaranteeing their quality use [19]. Based on our results, we recommend applying more effort to enhancing the ability of AS&Rs to learn the German language as a mid-to long-term strategy to overcome language barriers. Particular focus should be placed on female refugees, older refugees, and those with chronic diseases or disabilities. We also recommend providing translated medical leaflets for patients who ask for them and medical interpreting services. This would help them to understand information regarding the medicines they take, including whether or not these medicines contain alcohol or pork products. Having pharmacy staff demonstrate effective cross-cultural communication skills would also be helpful in addressing barriers and any other cultural issues that could be related to the access and use of medicines [22]. The barriers we have addressed in our study may also affect other cultural and linguistic minorities in diverse communities and not just refugees [22]. Overcoming these barriers requires the provision of more training and education that takes into consideration cross-cultural factors, not only for refugees, but also for physicians, pharmacists, and their staff [45].

Healthcare professionals should try to have a better understanding of the conditions of asylum seeker and refugee patients and recognize their perspectives on their treatments and diseases. This is crucial for any successful intervention among patients [54]. There is a need for studies that address other factors that might limit AS&Rs from accessing healthcare services in general and medicines in Germany; this includes cultural barriers and discrimination in healthcare.

Supplementary Materials: The following supplementary materials are available online at <https://www.mdpi.com/1660-4601/18/2/519/s1>, Table S1: An overview of the questionnaire, Supplementary File 1: Questions from the part of the questionnaire that focuses on barriers to accessing medicines among Syrian asylum seekers and refugees.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data available on request due to restrictions e.g., privacy or ethical. The data presented in this study are available on request from the corresponding author.

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BMJ Open Cross-sectional survey to describe medicine use among Syrian asylum seekers and refugees in a German federal state: looking beyond infectious diseases

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ABSTRACT

Objectives The aim of our study was to describe medicine use and document self-reported diseases or conditions for which medicines were used among Syrian asylum seekers and refugees (AS&Rs) in the German state of North Rhine-Westphalia (NRW). We examined in this study differences in the use of medicines among different age and sex groups of the study participants.

Setting Fifteen different refugee shared accommodation centres in the greater Cologne area, a community centre with a language school and consultation office, and other places frequented by the Syrian community.

Participants Syrian AS&Rs registered in NRW and residing in the city of Cologne or surrounding areas.

Primary outcome measures The prevalence of using at least one medicine in the 7 days preceding data collection, and the use of prescribed medicines and self-medication.

Results Of the 1641 Syrian AS&Rs who took part in our study, the overall 7-day prevalence of medicine use was 34.9%. Among adults, headache and hypertension were the most common indications that led to medicine use. By dose, hypertension (954 doses) and diabetes (595 doses) were the first and second most frequent indication. Among children, fever and cough were the most common indication; ibuprofen and hederæ helicis folium preparations were the most used medicines. Low prevalence was found of medicine use for the treatment of either infectious diseases or mental disorders.

Conclusion Among the Syrian AS&Rs in NRW who participated in the study, non-communicable diseases (NCDs) were common presumed causes of use of medication among adults. We encourage future studies to pay more attention to NCDs medicine use among AS&Rs. Researchers should also consider reaching AS&Rs who live in private housing and not limit studies only to newly arrived AS&Rs who live in shared accommodation centres.

INTRODUCTION

The profile of countries affected by conflicts has been gradually shifting, resulting in increasing displacement of populations with higher incomes and life expectancies.¹ Correspondingly, there has been a shift in the burden

Strengths and limitations of this study

- This is the first study to report comprehensively on medicine use, including prescription and self-medication, and indications among a group of asylum seekers and refugees in Germany.
- To increase generalisability of this study, we employed a combination of sampling methods and took into account key demographic variables (age and sex).
- The target population was involved in several stages of the research design and implementation. This has ensured that the study instruments were well adapted to the culture of the target population.
- The study was restricted to medicines used over the previous 7 days in order to maximise the participants' recall accuracy. However, using a limited time frame could have led to underestimating the use of medicines.
- A limitation of this study is related to the seasonal variation of medicine use. The study lasted for 6 months (July–December) capturing part of the seasonal variation expected annually.

of disease among displaced populations from infectious to chronic diseases.^{1,2} Studies have reported that non-communicable diseases (NCDs) were the most common health problems among asylum seekers and refugees (AS&Rs) in several countries.^{2,3} More generally, 7 of the 10 leading causes of deaths in 2019 globally were NCDs.⁴ In contrast to acute infectious diseases, pharmacotherapy for chronic diseases typically entails continuous expenditures and patient retention in lifelong care.⁵ Care for some NCDs involves high costs, including expensive medications and frequent laboratory tests.⁶ Disruptions and shortages of medicines pose a challenge for the NCDs care among AS&Rs in many countries.^{7,8}



Germany has received a large number of AS&Rs over the past decade. To date, research on the health status and medical care of AS&Rs in Germany largely focuses on mental disorders and infectious diseases. Bozorgmehr *et al* identified 52 articles in a systematic review covering 25 years of publications on AS&Rs health; of these, 30 focused on mental diseases, 12 on infectious diseases and 6 on access to healthcare services and mental diseases among children. One of the remaining four studies was a systematic review which also focused on mental diseases, while the other three studies covered various topics including access to healthcare services, mental diseases, infectious diseases and NCDs.⁹ The lack of research about NCDs among AS&Rs diverges from calls for better evidence about the burden of NCDs and interventions to tackle them in this population.^{1 2 10}

Articles 4 and 6 of the asylum seekers benefit act (Asylbewerberleistungsgesetz) restrict the access to healthcare services among asylum seekers in Germany to emergency medical care, treatment for acute and painful conditions, care during pregnancy and childbirth, vaccinations and other 'necessary preventive measures'. Asylum seekers can obtain regular access to healthcare through standard statutory health insurance once they receive refugee status. In addition to the system-related restrictions, AS&Rs face other obstacles when accessing healthcare services. According to a previous study that has explored the barriers to accessing medicines among Syrian AS&Rs, language barriers and the possibility of purchasing medicines without a prescription were the most common barriers.¹¹

Use of medicines is the most common intervention in healthcare. Medicines constitute an important part of disease prevention, treatment and management.¹² Previous studies have documented inequalities in healthcare utilisation, including medication use in comparisons between migrants and natives in Germany.¹³ Little is currently known about the use of medicines among AS&Rs in Germany. Kahl and Kühlein published two studies on prescription data among a sample of asylum seekers in one reception centre in Erlangen, Bavaria.^{14 15} One of these studies focused on antibiotics and the other on psychotropic medicines. Another study investigated healthcare utilisation, including medicines use, among asylum seekers in Halle, Saxony-Anhalt.¹⁶ These three studies were limited to prescribed medicines and none provided adequate information on the use of medicines for chronic NCDs. All medicines, including those used by self-medication, should be considered when estimating medicine use rates in a given population.¹⁷ There is an urgent need for studies that comprehensively describe the use of medicines—including all therapeutic classes—among AS&Rs for the prevention and treatment of various diseases, including NCDs.¹⁰

The overall aim of this study was to provide an understanding of medicines use and document self-reported disease or conditions for which medicines were used among Syrian AS&Rs registered in North Rhine-Westphalia

(NRW), Germany. This also includes describing the prevalence and patterns of medicine use and examine any differences in the use of medicines among different age and sex groups of the study participants.

METHODS

Study design and sample

The study took place in the state of NRW, Germany, between July and December 2019. This study was based on a cross-sectional survey. We were unable to obtain access to the disaggregated NRW census data of AS&R as our sample frame, and therefore, used quota sampling, in conjunction with convenience and snowball sampling; this is a common approach for studies with AS&R.¹⁸ We used multiple entry points into the Syrian AS&R community to reduce selection bias that could have resulted from snowball sampling. For the quota sampling, we divided the study population into strata according to age and sex. The fraction of each stratum was estimated using census data from the statistics office of NRW, which provided aggregated data on the age and sex distribution of Syrian AS&Rs in NRW. Further details regarding the study design, sampling methods and the participants are described in Aljadeeah *et al*.¹¹ Syrian AS&Rs of all ages who had their addresses registered in the state of NRW were eligible. The term asylum seeker included those who applied for asylum in Germany and their asylum application hasn't been approved yet or has been rejected. The term refugee included those whose asylum applications in Germany had been approved by the BAMF and those who were allowed to stay in Germany due to a ban on deportation.

Data collection

As described in Aljadeeah *et al*,¹¹ one researcher (SA) recruited participants from fifteen different refugee shared accommodation centres (RSACs) in the greater Cologne area, at a community centre with a language school and consultation office, and at other places frequented by the Syrian community, including Syrian restaurants and cafes, and during social events for the Syrian community.

A questionnaire (that was primarily composed of validated instruments and questions used in other studies) was used to collect data.^{19 20} Information about the use of medicines was collected using questions from the German Health Interview and Examination Survey for Adults (DEGS)¹⁹ and the German Health Interview and Examination Survey for Children and Adolescents (KiGGS).²⁰ The DEGS and KiGGS are national representative surveys that the Robert Koch Institute, the leading national health institute in Germany, has regularly conducted since 2008 and 2003. The DEGS and KiGGS aim to collect data on the health and health determinants, including medicines use, of the adult and children and adolescents in a representative sample of the general population in Germany.^{19 20} The DEGS and KiGGS survey instruments

Table 1 Seven-day prevalence of the use of at least one medicine, by user sex and age

		7-day prevalence of medicines use		
		n	Proportion of total (%)	
Total (n=1641)		573	34.9	
Adults (≥18 years) (N=1063)	Total	440	41.4	
	Sex	Male (n=711)	276	38.8*
		Female (n=352)	164	46.6*
	Age	18–29 (n=468)	127	27.1†
		30–39 (n=318)	140	44.0†
		40–49 (n=158)	82	51.9†
		50–59 (n=78)	56	71.8†
≥60 years (n=41)		35	85.4†	
Children (≤17 years) (N=578)	Total	107	18.5	
	Sex	Boys (n=313)	47	15.0*
		Girls (n=265)	60	22.6*
	Age	0–4 (n=171)	57	33.3†
		5–9 (n=170)	21	12.4†
		10–13 (n=115)	12	10.4†
14–17 (n=122)		17	13.9†	

*Difference is significant at the 0.05 level.

†Difference is significant at the 0.001 level.

are not publicly available, and they were accessed on a written request to the Robert Koch Institute. The survey was conducted in Arabic which is the official language in Syria. Arabic literacy among Syrian nationals is high (86.4%).²¹ Details about translating the questionnaire in this study are described in Aljadeeah *et al.*¹¹ Participants were invited to bring to the interview the original packages, package inserts and patient information leaflets of all the medicines they had used in the previous 7 days.

To collect data on medicine use, a researcher asked each participant the following question: ‘Did you use medicines or dietary supplements such as vitamins or minerals during the last seven days?’ The question was repeated until the participants did not mention any additional products. Dietary supplements were defined as products that contain a dietary ingredient, for example vitamins, minerals and amino acids.²² For each medicine a respondent mentioned using, we recorded the brand name, the International Non-proprietary Name, pharmaceutical dosage form (tablets, syrup, etc), the number of daily doses, intake duration, the reason for taking the medicine, the administration route and how it was obtained (options included: (1) prescribed by a physician; (2) purchased without a prescription; (3) family medicine cabinet (prescribed by a physician to someone other than the person taking it); (4) family medicine cabinet (medicine was purchased without a prescription) or (5) any other source). A follow-up

interview to gather missing information was arranged in cases when the participant did not bring all information for the medicines used in the past 7 days. The rest of the questionnaire, which included questions concerning sociodemographic characteristics, was self-administered. The questionnaire administered in digital form on tablet computers using the online survey tool Qualtrics.²³ For children who were younger than 14 years old, the questions were answered by parents. More information regarding the questionnaire and data collection can be found in Aljadeeah *et al.*¹¹ We could not perform a power calculation to determine the sample size for this study because no adequate data that reported the use of medicines among AS&Rs in Germany were available. We aimed for a relatively large sample size (1500 individuals). This was a pragmatic decision based on discussions with a biostatistician.

Variables

The 7-day prevalence was calculated as the proportion of AS&Rs who has used at least one medicine in the 7 days preceding data collection. Other variables of interest were respondents’ age and sex, the self-reported conditions or diseases that led to using medicines, the self-reported presence of chronic diseases and the use of prescribed medicines and self-medication. We differentiated between prescribed and self-medication on the basis of the answers to the question regarding the source of each recorded medicines (prescribed vs any other means, such as over-the-counter (OTC) purchase, provided by family members or friends, or other sources).

Data analysis

We stratified the sample into adults and children (the latter group included all participants younger than 18 years of age). We used the WHO’s Anatomical Therapeutic Chemical (ATC) Classification system (2020 version) to classify the medicines reported in this study.²⁴ Medicine consumption per therapeutic group is expressed in two forms: as a 7-day prevalence in adults and children and by the total number of doses for each medicine. From a drug utilisation research perspective, it is important to consider both the prevalence of medicine use and the number of doses, as the high number or frequency of medication doses is associated with medication burden among patients.²⁵ The relative use of medicines is presented by stratifying the total amount of medicines used by the sex and age of the participants and by whether the medicines were prescribed or not. In addition, we report the number of defined daily doses (DDDs) for each medicine. DDD is defined as: ‘the assumed average maintenance dose per day for a drug used for its main indication in adults.’²⁴ DDDs were calculated based on medicine use in adults.^{24 26} The number of packages was used as a measurement unit for medicine consumption among children and teenagers, as DDD is not an appropriate measure for those age groups.^{27 28}

Statistical analysis

We used Pearson's χ^2 test to examine the differences between sex and age groups in the 7-day prevalence of using at least one medicine and in using prescribed medicines and self-medication. We also used Pearson's χ^2 test to compare the proportions of adult participants who self-reported having chronic diseases in various sex and age groups. A $p < 0.05$ was considered indicative of statistical significance. All statistical assessments were performed using IBM SPSS Statistics V.25 (IBM).

Patient and public involvement

As previously reported by Aljadeeah *et al.*¹¹ to address challenges of conducting research with AS&R populations, and to enhance our understanding of the subject matter, we involved Syrian activists and other prominent members of the NRW Syrian community throughout the planning, execution and analysis of the study. Their support was particularly important in the recruitment of study participants. They also provided feedback on the findings and recommendations arising from the research.

RESULTS

Prevalence of medicine use in the study population

Of the 1641 Syrian AS&Rs included in the analysis, 1063 were adults and 578 were children (≤ 17 years). Males comprised 62.4% of the sample. The majority of participants lived in private housing (78.6%), while 20.5% lived

in RSACs. The average length of stay in Germany was 44.0 months. About 98% of the participants had health insurance. Information about other sociodemographic characteristics of the participants (health insurance status, employment status, education and income) can be found in online supplemental table 1. Among adult participants, the 7-day prevalence of using at least one medicine was 41.4%. A total of 6466 doses of 951 medicines had been taken in the 7 days preceding the data collection (see table 1). The prevalence of medicine use was higher among females (46.6%) than males (38.8%). An increase in the prevalence of medicine use was observed with increasing age: the lowest prevalence was among adult participants between 18 and 29 years (27.1%), and the highest was among those ≥ 60 years (85.4%).

Among the children, the prevalence of using at least one medicine was 18.5% and, in total, 738 doses of 135 medicines had been taken in the 7 days preceding data collection. The 7-day prevalence of medicine use was higher among girls (22.6%) compared with the boys (15.0%) (table 1). Unlike the adults, the youngest group of children (0–4 years) had the highest prevalence of medicine use.

Conditions that led to using medications

Among adult AS&Rs, headache was the most commonly reported reason for taking medicines (8.4%), followed by hypertension (6.7%) (table 2 shows the 10 most common

Table 2 The 10 most commonly reported conditions that led to use of medicines by adults and children

	Conditions that led to medicines use	No of participants who had this condition	Prevalence (%)	No of doses	No of different medicines taken for this condition
Adults (≥ 18 years) (N=1063)	Headache	89	8.3	275	8
	Hypertension	71	6.7	954	26
	Gastric pain	49	4.6	426	6
	Diabetes	44	4.1	595	11
	Dietary supplement	43	4.1	250	13
	Spinal pain	38	3.6	276	10
	Stroke prevention	30	2.8	203	3
	Hypothyroidism	30	2.8	215	3
	Influenza	26	2.5	175	12
	Allergies	22	2.1	109	9
Children (≤ 17 years) (N=578)	Fever	32	5.5	136	2
	Cough	23	4.0	134	3
	Influenza	18	3.1	89	3
	Dietary supplement	13	2.3	85	3
	Common cold	10	1.7	68	4
	Epilepsy	3	0.5	14	1
	Otitis media	3	0.5	33	4
	Asthma	3	0.5	21	3
	Headache	2	0.4	7	3
	Painful menstruation	2	0.4	6	1

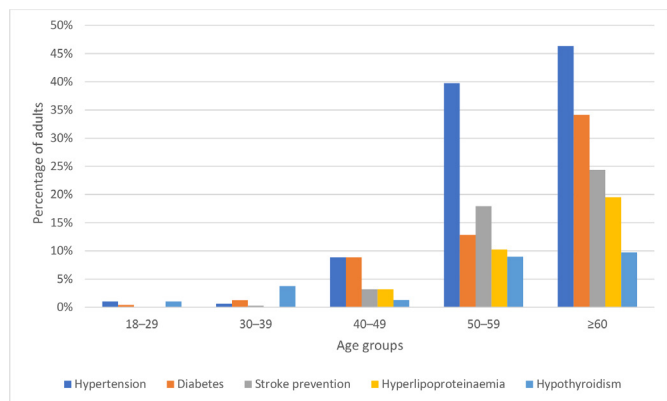


Figure 1 The five most common chronic conditions that led to medicine use among adult participants by age.

causes). The greatest number of individual doses of medicine were for hypertension (954 doses) and diabetes (595 doses). Four of 10 most commonly reported reasons for medicines use were chronic conditions: hypertension, diabetes, stroke prevention and hypothyroidism. In total, 13.7% of the adults stated that they had one or more chronic disease for which they took medicine. More females (17.9%) than males (11.7%) reported having chronic diseases for which they took medicines (online supplemental figure 1) and this difference was statistically significant ($p=0.006$). The proportion of participants who reported having chronic diseases increased with age (figure 1) and the differences between age groups were statistically significant ($p<0.001$). Among the 10 most common conditions that led to medicine use, one was infectious (influenza). None were mental disorders; 17 adults (1.6%) reported taking 181 doses of 21 psychotropic medicines for mental diseases.

Among children, fever (5.5%) and cough (4.0%) were the most common conditions that led to medicine use (table 2). We found that 1.6% of the children had taken medicine for chronic diseases, and 2 of top 10 causes for medicine use were chronic diseases (epilepsy and

asthma). Of the remaining eight most frequent causes of use of medicines, four were infectious diseases (influenza, cough, common cold and otitis media). None of the children took medicine to treat mental diseases.

Patterns of medicine use by ATC group

Among adults, the highest prevalence of medicine use (14.6%) was for medicines for the alimentary tract and metabolism (ATC code A); this was followed by medicines of the musculoskeletal system (M) (13.4%), the nervous system (N) (12.4%) and the cardiovascular system (C) (8.0%). The prevalence of medicine use in these groups varied between males and females. Among males, medicine use from the M group (13.8%) was highest compared with the other ATC groups, followed by group A medicines (13.5%). Among females, the prevalence of medicine use in group A was the highest (16.8%), followed by group N medicines (12.8%) (online supplemental figure 2).

The prevalence of medicine use by ATC group also varied between the different age groups. Among participants in the 18–29 and 30–39 age groups, the prevalence of group M medicines use was highest (7.5% and 15.7%, respectively). In the 40–49 and ≥60 years age groups, use of group A medicines had the highest prevalence (22.8% and 63.4%, respectively). In the 50–59 age group, group C medicines had the highest prevalence (42.3%) (figure 2).

Among the children, the prevalence of group M medicine use was the highest (8.1%), followed by those in the respiratory system (ATC code R) (4.7%), and the medicines of groups N and A (3.5% and 2.6%, respectively). Among both boys and girls, the prevalence of group M medicine use was highest (6.07% and 10.6%, respectively) (online supplemental figure 2). The prevalence of use of group M medicines was the highest among all age groups of the children (figure 2).

The most frequently used medicine among adults was ibuprofen, which was used by 10.4% of adults, followed by paracetamol (6.8%) and omeprazole (3.1%). Ibuprofen

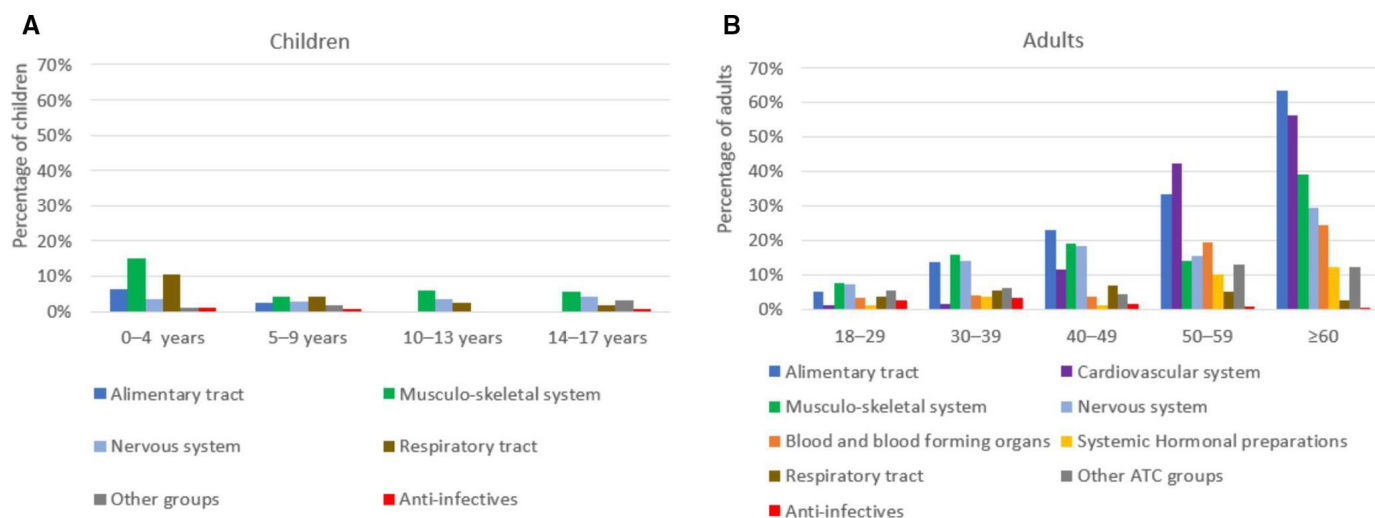


Figure 2 Prevalence of use of medicines from the main ATC groups among adult and child study participants, by age group. ATC, anatomical therapeutic chemical.

**Table 3** Prescribed or self-medication use among adult and child participants, by sex and age

			Prescribed medication		Self-medication		Both	
			n	%	n	%	n	%
Total			333	20.3	158	9.6	55	3.4
Adults (18<=)	Total		277	26.1	108	10.2	55	5.2
	Sex	Male	175	24.6*	76	10.7	25	3.5
		Female	102	29.0*	32	9.1	30	8.5
	Age	18–29	76	16.2†	42	9.0*	9	1.9
		30–39	71	22.3†	48	15.1*	21	6.6
		40–49	58	36.7†	12	7.6*	12	7.6
		50–59	41	52.6†	5	6.4*	10	12.8
		≥60	31	75.6†	1	2.4*	3	7.3
Children (<18)	Total		56	9.7	50	8.7	1	0.1
	Sex	Boys	26	8.3	20	6.4	1	0.3
		Girls	30	11.3	30	11.3	0	0
	Age	0–4	29	17.0	27	15.8	1	0.6
		5–9	14	8.2	7	4.1	0	0
		10–13	6	5.2	6	5.2	0	0
		14–17	7	5.7	10	8.2	0	0

*Difference is significant at the 0.01 level.

†Difference is significant at the 0.001 level.

was also the medication with the highest number of doses used (9.7%), followed by metformin (for diabetes) (5.1%) (online supplemental table 2). Among the children, ibuprofen was also the most used medication (8.1%), followed by hederæ heliçis folium (the active ingredient in expectorant preparations) (3.1%) and paracetamol (2.3%) (online supplemental table 2).

Prescribed medication, self-medication and sharing of medications

Of the 1086 medicines recorded in the study, 824 (75.9%) were prescribed by physicians and 262 medicines (24.1%) were used by self-medication. Of the 951 medicines used by the adults, 78.7% were prescribed by physicians and 21.3% were used by self-medication. Fewer adult males used prescribed medicines compared with females (24.6% vs 29.0% respectively, $p=0.002$). The prevalence of self-medication was only slightly higher among males than females (10.7% and 9.1%, respectively, $p=0.147$) (table 3).

The prevalence of prescription medication use increased with age. Self-medication varied among age groups, with the highest prevalence among participants in the 30–39 age group (15.1%) and the lowest in those ≥60 years (2.4%) (table 3).

Among the children, 56.3% of the 135 medicines used were prescribed by physicians and 43.7% were used by self-medication. The prevalence of using medicines by self-medication was higher among girls than boys (11.3% and 8.3%, respectively; $p=0.051$) (table 3). The prevalence of use of prescribed medicines was higher among the 0–4

age group (17.0%) when compared with the other childhood age groups. The prevalence of using medicines by self-medication was also higher among the 0–4 age group (15.8%) when compared with the other childhood age groups ($p=0.14$) (table 3).

Among adult participants, 37 adults (3.5%) shared 37 medicines with other people. Of the 37 medicines, 16 were OTC medicines. The remaining 21 medicines were prescription-only medicines. Fourteen adults (1.3%) used medicines that had been imported and not purchased in Germany. Among the children, 32 (5.5%) shared 32 OTC medicines with other people (online supplemental table 3).

DISCUSSION

In Germany, there is a lack of routine reporting on the health status and quality of medical care, including medication use, among AS&Rs. Empirical studies are needed to provide evidence to improve policy and clinical practice with this population.⁹ To our knowledge, this is the first study to report comprehensively on medicine use and indications among a group of AS&Rs in Germany.

This study contributes new insights about medication use among Syrian AS&Rs. First, the use of medicines for NCDs was relatively common among adults, with hypertension being the second-most common condition that led to their use of medicines. Treating two chronic diseases, hypertension and diabetes, led to using the highest number of doses of medicine in the study period. Second, although acute conditions, such as fever and cough, were

the most common reasons for children's medicines use, overall we found a low prevalence of use of medicines, including antibiotics, for infectious diseases. Third, the prevalence of psychotropic medicine use was also low in our study. These and other findings have meaningful implications for both policy and clinical medical practice.

Among adult participants, the 7-day prevalence of using at least one medicine was 41.4%. The 2008–2011 DEGS study described medicines use in a representative sample of the German adult population and found that the 7-day prevalence for using at least one medicine reached 74.4%.¹⁷ This is not unexpected because the Syrian AS&R study population was overall younger than the DEGS study population. Another possible reason for the different rates of medicine use is related to lower utilisation of healthcare services among AS&Rs compared with German citizens with statutory health insurance. Barriers that limit AS&Rs' access to healthcare services, including language barriers and limited knowledge about the health system in Germany, are some of the reasons that may explain the results; this area should be further explored.¹⁵ Similar to our study, the DEGS and KiGGS studies reported medicines use in the last 7 days prior to data collection and included both prescribed medicines and self-medication in the general population. However, comparing the results of our study with the results of the DEGS and KiGGS should be considered with caution. The DEGS and KiGGS studies comprised the entire country whereas our study took place in one state (Land). In addition, our survey was conducted in 2019, while the DEGS and KiGGS surveys were conducted in 2008–2011 and 2014–2017, respectively.

In our study, the prevalence of medicine use was higher among females, which could be explained by the higher proportion of female participants who self-reported having one or more chronic disease. The prevalence of medicine use increased with age, which is also likely related to the higher prevalence of chronic conditions in older age groups. The DEGS study also found that prevalence was higher among females and increased with age. Medicine use among the 18–29 years old in our study was also considerably lower than in the DEGS study (27.1% vs 61.2%, respectively). However, the differences between German natives and AS&Rs steadily decreased with increasing participant age, with little difference in the over 60 age groups.

Among the children in our study, we found that the 7-day prevalence of using at least one medicine was 18.5%. Prevalence was higher among girls; children in the 0–4 age group had the highest prevalence of medicine use, followed by those in the 14–17 age group. For comparison with the general population, the 2014–2017 KiGGS study on medicine use in a representative sample of German children from 3 to 17 years old reported a 36.4% prevalence of use of at least one medicine in the previous 7 days. The prevalence in the KiGGS study was similarly higher among girls.²⁷ By age, the highest prevalence occurred in the 14–17 age group. However, the

KiGGS study did not include children younger than 3 years of age.

Hypertension was the second-most common condition that led to medicine use among adults, and 4 of the 15 most commonly used medicines among adults were for the treatment of hypertension (namely, amlodipine, hydrochlorothiazide, candesartan and ramipril). Hypertension and diabetes were the two diseases that led to the highest number of medication doses. Our results are consistent with studies that have reported high prevalence of both hypertension and diabetes among Syrian refugees in Jordan, Lebanon, Turkey and other countries in Europe.^{3 10 29} NCDs were also the diseases that most commonly led to medicine use among the adult German population.³⁰

Our study found a low prevalence of medicine use for the treatment of infectious diseases in adults. Influenza was the only infectious disease among the ten most common causes for medication use, and amoxicillin was the only antibiotic among the 15 most commonly used medicines by adults. Amoxicillin was also found to be the most commonly prescribed antibiotic for a group of asylum seekers in the city of Erlangen,¹⁴ and is the most commonly prescribed antibiotic for Germans with statutory health insurance.³¹ The low prevalence of medicine use to treat infectious diseases is consistent with several other studies on the prevalence of diseases among Syrian refugees in Germany and other countries. One study reported a very low prevalence of tuberculosis among Syrian AS&Rs in Germany compared with AS&Rs from other nationalities.^{32 33} Another study that investigated the health status of AS&Rs in the state of Bavaria showed a low prevalence of infectious diseases (4.8%) among Syrians.³⁴ In 2013, an increase in the incidence of 13 infectious diseases was expected in Turkey following the start of the conflict in Syria. However, since the influx of 3.5 million Syrian refugees to Turkey, there have been increases in cases of leishmaniasis and measles, but no significant increases in other infectious diseases have been detected.³⁵ A study from Australia has also reported a low prevalence of infectious diseases among Syrian AS&Rs.³⁶ Given the apparently low prevalence of infectious diseases among Syrian AS&Rs, it is not surprising that our study found low rates of use of medicines for these diseases.

Our results on the frequency of prescription medicine use (78.7%) and self-medication (21.4%) are similar to the DEGS study, in which 71.8% of the medicines used over a 7-day period were prescribed by a physician and 27.7% were used by self-medication.¹⁷ Among children in our study, 56.3% of medicines used were prescribed by physicians, and 43.7% were self-medication. Results from the KiGGS study also showed that children used more prescription medicines than self-medication.³⁰ A similar outcome was reported in a study that focused on medicine use among child refugees in England.³⁷

There was little antibiotic use reported in our study. This finding contrasts with studies by Kahl and Kühlein



who reported a high proportion of antibiotic prescriptions for asylum seekers in Erlangen. However, the authors did not provide either the reasons for prescribing antibiotics or the nationality or sex of their study population.^{14 15} Factors such as country of origin have considerable effects on refugees' health, and this factor may account for our divergent findings.²⁹ Syrian AS&Rs present with different demographic profiles and disease burden than, for instance, AS&Rs from some African countries where a disease such as cholera would be more prevalent.¹⁰ Another factor that could explain differences between our results and those of Kahl and Kühlein may be due to their sample, which was limited to newly arrived asylum seekers. In Kahl Kühlein, the average period of stay in the reception centre was 46.9 days while the average stay of our participants in Germany was 44.0 months. The duration of stay in a host country can play a role in the health status of AS&Rs—over a longer period of stay, AS&R health profile tends to converge with that of the host country's population.^{29 32}

Housing status is an important social determinant of health.³⁸ Studies that have previously reported on the health status and utilisation of healthcare services among AS&Rs in Germany were based on data collected in RSACs.^{9 14–16} This could be connected to difficulties in collecting reliable data on the health status of AS&Rs living in private housing.³⁹ Living in RSACs is related to higher levels of distress.⁴⁰ While other studies have provided valuable information about the health status and the use of medicines among those asylum seekers who live in RSACs, their findings cannot be generalised to the majority of the AS&R population in Germany. By 2018, approximately 75% of AS&Rs in Germany lived in private apartments.⁴¹ For this study, we intentionally sought to reach AS&Rs who lived in private housing. As 78.6% of our participants lived in private housing, we believe that our study group was more representative of the Syrian AS&R population than other studies, which were limited to AS&Rs living in RSACs.

Prior studies have described a high prevalence of mental disorders, such as post-traumatic stress disorder, among different groups of AS&Rs in Germany.^{9 42} However, the prevalence of psychotropic medicine use was low in our study. Kahl and Frewer suggested that the prescription rates for psychotropic drugs were also under-represented in their study compared with the higher prescription rates of these medicines among the German population.¹⁵ Of course, some psychotherapeutic interventions do not involve pharmacotherapy. However, access to these therapies among AS&Rs is clearly also limited due to language barriers. Pharmacotherapy to manage mental disorders remains a feasible choice for AS&Rs in Germany.¹⁵ Reasons for the low prevalence of psychotropic medicines use found in our study could be related to various barriers to accessing mental health services among AS&Rs. These include language barriers, lack of information about the existence of mental health services, and stigma around seeking mental health services.⁴³ The low prevalence of

psychotropic medicine in our study should be further examined to determine whether Syrian AS&Rs have been neglected by mental health services.¹⁵

The management of NCDs such as hypertension and diabetes require adherence to continuous pharmacotherapy and frequent laboratory tests, which poses a challenge for AS&Rs in many countries.^{5–8} Currently, infectious diseases received the most attention of the policy and clinical practice related to AS&Rs compared with the management of NCDs.²⁹ In Germany, asylum seekers of all nationalities are obliged to participate in chest X-ray examinations to screen signs of potentially infectious pulmonary tuberculosis (except for pregnant women and children younger than 15 years of age).³³ Policies in Germany should account for the different regions where AS&Rs come from and the burden of diseases that could vary between these regions. Since 2015, the chest X-ray screening for tuberculosis for Syrian asylum seekers in the Netherlands was suspended as the tuberculosis incidence in Syria was low (<50 cases per 100 000 people). Limiting this screening to asylum seekers from high-incidence countries could improve cost-effectiveness.⁴⁴ The resources and efforts paid to X-ray screening for tuberculosis among Syrian AS&Rs can be invested instead in the prevention and management of NCDs. The high prevalence of medicines use for hypertension and diabetes in our study raises the question of whether enough attention has been paid to develop policies and clinical practices to ensure NCDs care in the Syrian AS&R population. This outcome of our study also indicates the need to rethink the healthcare policies for AS&Rs populations in a decade when the largest displacement emergency in the world has happened in Syria, a country with a high burden of NCDs.¹⁰ Additional efforts are needed to raise awareness about the prevention and management of NCDs among AS&Rs.

Strengths and limitations

The complexity of AS&R health statuses makes it difficult to generalise research findings from one group to the wider populations of AS&Rs.²⁹ To increase generalisability of our study, we employed a combination of sampling methods and took into account key demographic variables (age and sex) during the design of the sample. Furthermore, study recruitment was not limited to RSACs.

This study had a number of strengths. By collecting primary data, we were able to comprehensively report on the use of medicines among Syrian AS&Rs, including prescription and self-medication. We were also able to record the diseases and conditions that led to using medicines. Since we relied on self-reported medicine use, we asked participants to bring to the interview original packages, package inserts and patient leaflets for their medicines to minimise recall bias. However, the possibility of recall bias cannot be excluded.⁴⁵ We validated participants' answers by reviewing the package information. We did not use prescriptions or claims data—as many

other studies have—to avoid focusing only on medicines that were prescribed or covered by health insurance. By using self-reporting, we covered both prescription and self-medication, and determined actual consumption.¹⁷ Another strength of our study was the involvement of our target population in several stages of the research design and implementation. Participation of AS&R community members ensured that the study instruments were well adapted to the culture of the target population.

Our study was restricted to medicines used over the previous 7 days in order to maximise the participants' recall accuracy. However, using a limited time frame could have led to underestimating the use of medicines. For example, there may be medications that are often taken by participants, but which had been interrupted during this time frame.¹⁷ Severely ill AS&Rs who might have been hospitalised could not participate in our survey. This might have led to the underestimation of medicines use in our study population. Our study was limited to one state (NRW), while the DEGS and KiGGS studies comprised the entire country. In Germany, there are variations in the prevalence of medicine use between the different states.¹⁷ Another limitation of this study is related to the seasonal variation of medicine use. The study lasted for 6 months (July–December) capturing part of the seasonal variation expected annually. Future studies should consider annual seasonal variation. Finally, the number of participants in the ≥60 age group, which had been estimated based on census data, was relatively small. To achieve a better understanding of medicine use among this age group, future studies should focus on this age group.

CONCLUSION

Studies have documented an epidemiological shift, from infectious diseases to NCDs, among AS&Rs as among general populations in many countries. However, previous research with AS&Rs populations in Germany has focused on mental disorders and infectious diseases. Studies on the use of medicines for NCDs and other diseases are still scarce. This study provided a detailed look at the use of medicines among a large sample of AS&Rs living in short-term and long-term accommodations and found that adult AS&Rs commonly used medicines for the treatment or management of NCDs. We encourage future studies to pay more attention to detection, treatment and management of NCDs among AS&Rs in Germany, including those who live in private housing.

This and other similar studies can inform and improve national and international policies and plans to prevent, control and reduce the burden of NCDs among AS&R populations. We further strongly encourage the involvement of AS&Rs in health research focused on their communities. Through regular interactions with AS&R communities at all stages of research projects, researchers can improve the quality, value and relevance of their research.

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Article

Outpatient Antibiotic Dispensing for the Population with Government Health Insurance in Syria in 2018–2019

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Abstract: Little is known about antibiotic uses at the population level in Syria. The aim of our study is to present outpatient antibiotic dispensing (OAD) patterns and rates for patients with health insurance in the parts of Syria that are controlled by the Syrian government using different indicators. Outpatient data on all dispensed antibiotics for 81,314 adults with health insurance were obtained and stratified according to age, sex, governorate and annual season. OAD was mainly expressed as the number of defined daily doses (DDDs) per 1000 people per day (DID). OAD patterns were assessed according to the anatomical therapeutic classification (ATC) and the Access, Watch and Reserve (AWaRe) classification. OAD was 20.13 DID. Amoxicillin/clavulanic acid and clarithromycin were the most dispensed antibiotics (5.76 and 4.4 DID, respectively). Overall, a predominant consumption of broad-spectrum antibiotics was noted. The Watch group of the AWaRe classification had the biggest percentage of OAD (13.26 DID), followed by the Access and the Reserve groups (6.55 and 0.17 DID, respectively). There was a significant difference in OAD between the sex and age groups. The seasonal and regional variations in OAD were also significant. Broad-spectrum antibiotics dispensing was high compared to other studies from different countries. These results are concerning, as they can contribute to antibiotic resistance.

Keywords: antibiotics; outpatient; dispensing data; Syria; demography

1. Introduction

Antibiotics play an essential role in controlling infectious diseases [1]. However, the use, including misuse and overuse, of antibiotics is one of the main factors contributing to the development of antibiotic resistance. This has reduced the treatment options for infectious diseases, jeopardizing global public health [2].

In Europe and North America, outpatient antibiotic dispensing (OAD) is often prescription-only [3] but can be accessed without prescriptions in many countries of the global South [4,5]. In 1988, Syria's Ministry of Health legislated to determine which drugs could be sold over-the-counter. Antibiotics were not included [6]. However, a lack of enforcement of the laws and guidelines and community pharmacists' financial interests have led to the common practice of dispensing antibiotics over-the-counter in Syria [7]. Another challenge related to the accessibility of antibiotics in Syria is linked to the ongoing conflict situation. This conflict has increased the prevalence of penetrating traumatic injuries with contaminated open wounds and fractures. Antibiotics are required to treat these injuries, usually for prolonged periods [8]. The conflict has also caused the epidemic spread of infections through vulnerable populations [9].

Health indicators have improved considerably in Syria, and the pharmaceutical sector developed successfully during the three decades before the conflict [10–12]. Since 2011, millions of civilians have borne the brunt of this conflict, with nearly one in three of the population (6.2 million out of 21 million) forced to leave their homes between 2011 and 2018. Two-thirds of the population in Syria live below the poverty line. The continuing conflict and internal displacement have had severe consequences for Syria's health system [12]. Less than half of public health care facilities were fully functioning in 2018. Tens of thousands of injured Syrians have died or sustained lifelong disabilities, having been unable to access medical assistance [13].

Healthcare in Syria is financed by public funds and private insurance. Out-of-pocket expenditures on outpatient consultations and medicines is common [14]. No national health insurance is available to cover all inhabitants in Syria. However, individuals working in public organizations, some ministries and professional associations are provided with health insurance [15]. Private insurance companies have provided individual and group health plans since 2004 [16]. The total number of people with health insurance in Syria reached 841,852 by 2019; most of them (79%) are employed by the government [17].

The use of antibiotics has been intensively studied due to the public health consequences related to their widespread use [18]. Despite Syria's high rates of antibiotic resistance and the need for antibiotic stewardship [8], insufficient data are available regarding the patterns of antibiotic consumption [19]. Few studies have examined nonprescription access to antibiotics in Syria, and those published were limited to certain settings, such as universities and or larger urban areas, e.g., Aleppo and Damascus [7,20,21]. None described the patterns or calculated the quantities of used or dispensed antibiotics.

This study aims to present OAD patterns and rates for patients with health insurance using different indicators. We performed additional analyses to explore potential associations between the antibiotic dispensing rates and demographic factors, such as age and sex, and assess any seasonal or regional variations.

2. Methods

2.1. Setting and Data Source

This study is based on outpatient dispensing data from thirteen Syrian governates, excluding the Ar-Raqqa governorate, which is not under the Syrian government's control. We used health insurance data covering 12 months from June 2018 to May 2019 to express annual OAD patterns and rates and to include only one influenza winter peak per the 12-month period [18]. Health insurance data included the drug name, number of dispensed units, pharmaceutical form and administration route of the drug, prescription number, date of dispensing, the name of the governorate where the antibiotic drug was dispensed and each patient's age and sex.

2.2. Study Population

This study included the outpatient dispensing data of 81,314 beneficiaries. These beneficiaries were either employed by the Syrian government and covered by the health insurance scheme, members of professional associations or privately insured university students. Government employees belong usually to Syria's middle-income class [22].

2.3. Data Analysis

The data in this study included all medicines dispensed for the study population. We included only medicines classified in the anatomical therapeutic chemical (ATC) classification as J01 (antibacterials for systemic use). We used the World Health Organization (WHO) ATC/DDD (defined daily dose) methodology to describe the antibiotic dispensing patterns (Version 2020). The defined daily dose (DDD) is "the assumed average maintenance dose per day for a drug used for its main indication in adults" [23]. DID stands for the number of defined daily doses per 1000 inhabitants per day. OADs were presented

by pharmacological subgroup (ATC3) and chemical substance (ATC5). The relative dispensing of antibiotics was presented as a percentage of the total dispensing by route of administration (oral or parenteral) and AWaRe categories (Access, Watch and Reserve). The Access category includes 48 antibiotics that are associated with a lower potential for antimicrobial resistance and recommended as the first and second choices for treating infections. The Watch category includes 110 antibiotics with a higher potential for antimicrobial resistance. The Reserve category includes 22 antibiotics. The antibiotics of the Reserve group are considered as a “last resort” to treat infections with multidrug resistant bacteria. They should only be applied when all other alternatives have failed to treat an infection. Stewardship programs should focus on antibiotics of the Watch and Reserve groups [24]. Some dispensed antibiotic combinations were not listed in the WHO AWaRe classification. We classified this group of antibiotics as “Not classified”. We used the drug utilization 90% methodology to rank antibiotics by volume of DIDs and specify which antibiotics account for 90% of the total dispensing [25]. We presented the volume of the OAD using the following indicators: total number of packages, DDD and DDD per 1000 inhabitants per day (DID). We adjusted DID by patient characteristics (sex and age). To adjust the number of DID by governorate, we calculated the number of DDDs per 1000 dispensing events in each governorate per day (DDED), since one beneficiary could receive antibiotics in several governorates. We also adjusted the number of DIDs for season by calculating the number of DDDs per 1000 inhabitants per day (out of 91 days).

2.4. Statistical Analysis

All statistical assessments were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) [26]. The significance of differences between the variables was assessed using nonparametric testing, as the dispensing data showed some evidence of a skewed distribution. A *p*-value of 0.05 was used as a cut-off for significance. We used the Mann–Whitney test to examine the significance of the differences between the medians of the OAD rates among females and males. We used the Kruskal–Wallis nonparametric ANOVA to examine the significance of the differences between the medians of the OAD rates in the different age groups, regions or seasons.

2.5. Ethical Considerations

Each patient was given a unique identifier number, but individual patients could not be identified. We secured approval from the ethics commission of the University of Bayreuth, who stated that analysis and reporting of the dispensing data in this study did not require their approval.

3. Results

This study is based on the outpatient dispensed medicines for 81,314 beneficiaries covered by health insurance in Syria. All these beneficiaries are adults ($18 \leq$). Of these, 33,444 patients (41.13%) received at least one antibiotic as outpatients between 1 June 2018 and 31 May 2019. The patients' mean age was 44.76 years: 22,383 (66.9%) were female, and 11,061 (33.1%) were male. The Supplementary Table S1 includes the number of patients in the different sex and age groups. The total number of the OAD packages reached 76,774. The highest number of antibiotic packages dispensed for a single patient was 22. The total number of OAD DDDs is 59,7518.81, and the total number of OAD DIDs was 20.13.

The most frequently dispensed antibiotic was amoxicillin/clavulanic acid (5.76 DID), followed by clarithromycin (4.4 DID). Nine antibiotics accounted for 90% of the total dispensed antibiotics (Table 1).

Table 1. Outpatient antibiotic dispensing rates that accounted for 90% of total dispensed antibiotics among adults with health insurance in Syria expressed in the number of defined daily doses (DDDs) per 1000 people per day (DID). AWaRE: Access, Watch and Reserve.

Number	Antibiotic	AWaRe	DID	Proportion of Total DID
1	Amoxicillin/Clavulanic acid	Access	5.76	28.62%
2	Clarithromycin	Watch	4.4	21.87%
3	Cefixime	Watch	2.66	13.05%
4	Cefuroxime	Watch	1.85	9.17%
5	Levofloxacin	Watch	1.09	5.4%
6	Azithromycin	Watch	0.72	3.59%
7	Cefdinir	Watch	0.63	3.15%
8	Cefprozil	Watch	0.55	2.71%
9	Ciprofloxacin	Watch	0.51	2.55%
Drug Utilization 90% (DU90%) 1–9			18.14	90.11%
Others 10–53			1.99	9.89%
Total			20.13	100%

Considering the number of dispensed antibiotics packages, 85% of the OAD in this study were for oral administration. The remaining 15% were for parenteral administration. Considering the number of DIDs, 98.6% of OADs were for oral administration, and 1.4% were for parenteral administration. Amoxicillin/clavulanic acid was the most dispensed oral (28.96%), followed by clarithromycin (22.17%). Ceftriaxone was the most dispensed antibiotic for parenteral administration (34.27%), followed by ceftriaxone and sulbactam (31.32%). Cephalosporines were the most dispensed group of antibiotics (ATC4), followed by penicillins. Table 2 lists the OADs divided by the pharmacological groups

Table 2. Total outpatient antibiotic dispensing rates among adults with health insurance in Syria according to the pharmacological group (ATC4) and expressed in DID.

Pharmacological Group	DID	Proportion of Total DID
Cephalosporins (J01D)	6.14	30.49%
Penicillins (J01C)	6.01	29.87%
Macrolides, lincosamides and streptogramins (J01F)	5.19	25.78%
Quinolones (J01M)	2.08	10.31%
Other antibacterials (e.g., linezolid, metronidazole and nitrofurantoin) (J01X)	0.46	2.29%
Tetracyclines (J01A)	0.14	0.6%
Aminoglycosides (J01G)	0.06	0.29%
Sulfonamides and trimethoprim (J01E)	0.04	0.21%
Combinations of antibacterials (J01R)	0.01	0.06%
Total	20.13	100%

3.1. Variation of Dispensed Antibiotics According to Patients' Demographic Characteristics

A statistically significant difference was observed in OAD rates between female and male patients ($p = 0.003$). The adjusted DID rates of OADs were higher among female patients (21.58 DID) than male patients (17.76 DID).

A statistically significant difference was observed in OAD rates between the different age groups ($p < 0.001$). Adjusted OAD rates were the highest among the patients aged 30–39 (25.07 DID) and the lowest among the patients aged 60–69 (14.37 DID).

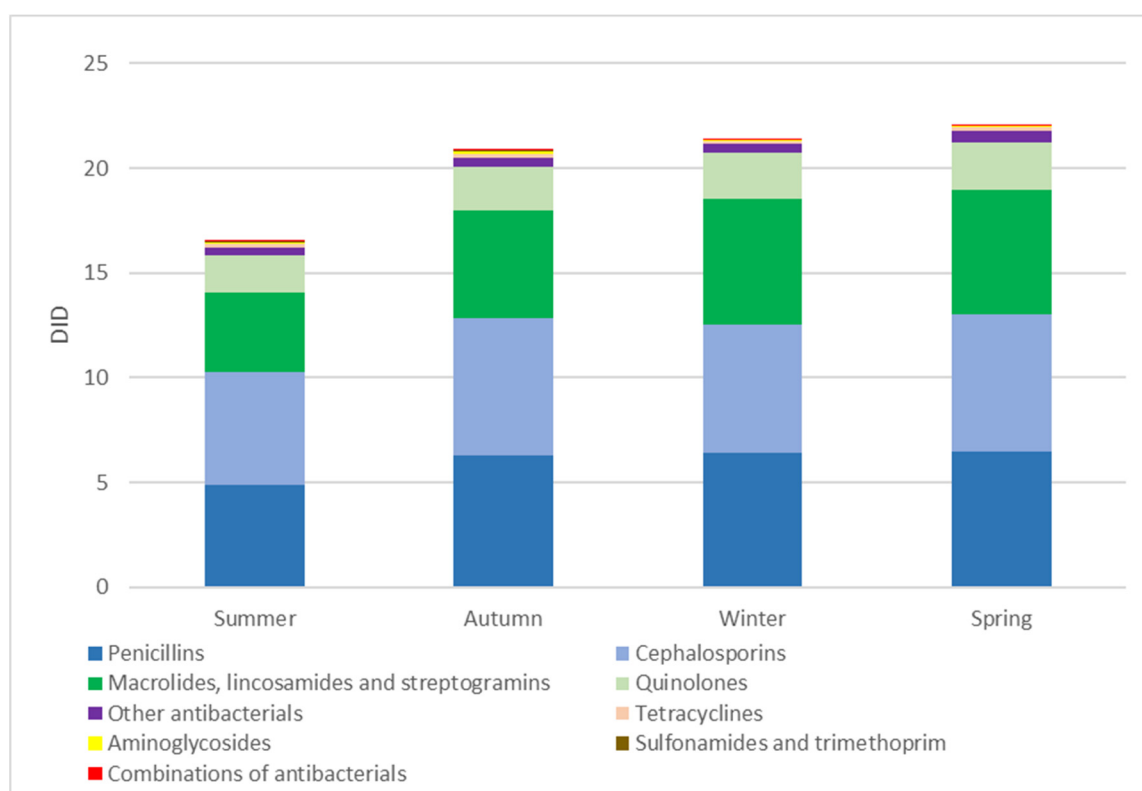
The antibiotics in the Watch category of the AWaRe classification had the highest percentage of OAD in this study (65.86%), followed by Access antibiotics (32.54%). Antibiotics in the Reserve category had a smaller percentage (0.83%). The remaining antibiotics (0.76%) were not classified (Table 3).

Table 3. Total outpatient antibiotic dispensing rates among adults with health insurance in Syria according to the AWaRe classification and expressed in DID.

AWaRe	DID	Proportion of Total DID
Access	6.55	32.54%
Watch	13.26	65.86%
Reserve	0.17	0.83%
Nonclassified	0.15	0.77%
Total	20.13	100%

3.2. Seasonal Variation

A significant difference was observed in OAD rates between the different seasons ($p < 0.001$). OAD rates were highest in the spring (22.05 DID), followed by the winter (21.36 DID) and autumn (20.84 DID). The antibiotic dispensing rates were lowest in the summer (16.49 DID) (Figure 1).

**Figure 1.** Total outpatient antibiotic dispensing rates (DID) among adults with health insurance in Syria by pharmacological group (ATC4) and season. DID: the number of defined daily doses (DDD) per 1000 people per day.

3.3. Regional Variation

During the study period, a significant difference ($p < 0.001$) in the total OAD was observed between Syria's different governorates that are under control of the Syrian government (Figure 2). According to the number of DDEDs in each governorate, Idlib (16.33 DDED), Quneitra (14.55 DDED) and Deer el-Zour (14.32 DDED) had the highest OAD rates, while Tartous (5.83 DDED), Lattakia (4.5 DDED) and Al-Suwayda (3.63 DDED) had the lowest OAD rates (Figure 3).

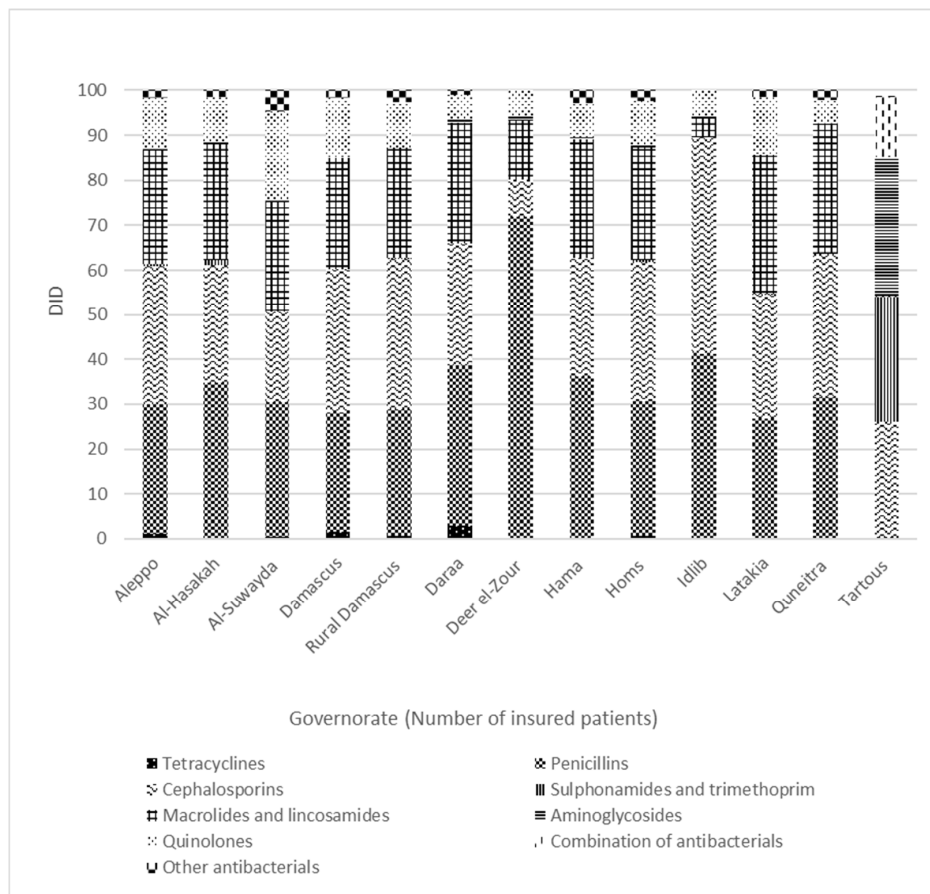


Figure 2. Proportional outpatient antibiotic dispensing (DID%) among adults with health insurance in Syria by pharmacological group (ATC4) and governorate.

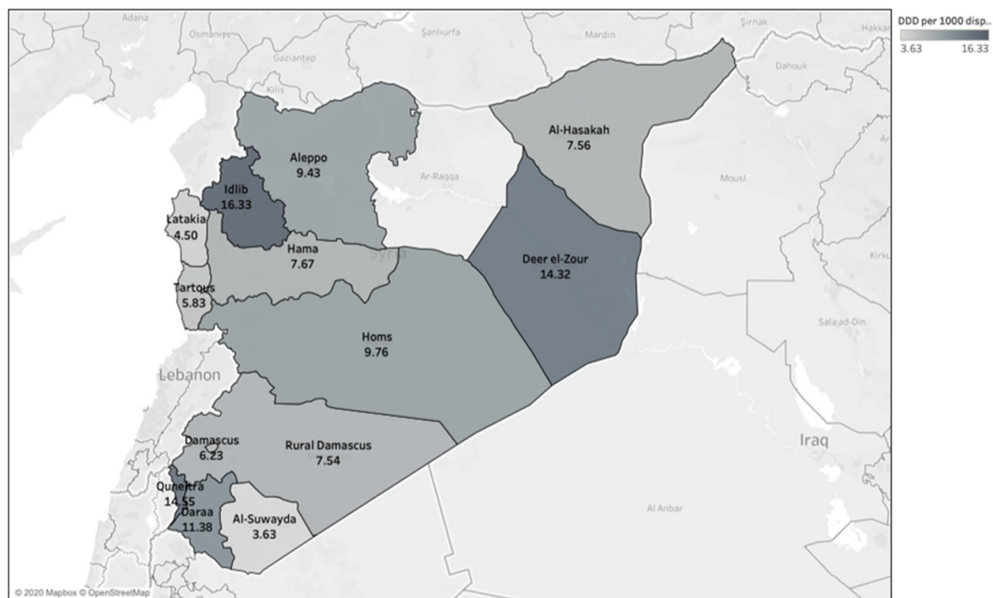


Figure 3. Adjusted outpatient antibiotic dispensing rates (DDD/1000 dispensing events/day) among adults with health insurance in Syria by governorate.

4. Discussion

To our knowledge, this is the first study to have used different indicators to describe the patterns and present the quantities of dispensed antibiotics using health insurance data with a large sample (81,314 beneficiaries) over a period of 12 months.

Our results show that the total OAD rate reached 20.13 DID. Borg et al. have reported high levels of antibiotic consumption in hospitals in the southern and eastern Mediterranean regions [27]. Many studies have reported over-prescriptions of antibiotics in middle- and low-income countries [28–30]. The WHO report on the Surveillance of Antibiotic Consumption showed that the total antibiotic consumption rates in Turkey and in Iran are among the three-highest antibiotic consumption rates of the 65 countries included in the study [31]. A comparison of the antibiotic dispensing rates in our study with those of such a report is not appropriate, because this report was not limited to outpatient dispensing data for adults, as in our study [29]. Studies reporting antibiotic dispensing in outpatient settings from low- and middle-income countries are scarce, making it difficult to compare our data with those of studies that used the same settings. Comparing the OAD rates in our study with the OADs in European countries, the rates in our study are higher than the average OAD rates in these countries in the years 2017/2018 (18.4 DID) [32]. We should mention that the OAD data from the European countries included children's OAD data, which also limited the direct comparison of these data to those in our study.

The WHO report showed that penicillins are the most dispensed antibiotics in 62 of the 65 countries included in the study [31], while cephalosporines were the most dispensed antibiotics in our study. This can be explained by these factors: (1) the high prevalence of antimicrobial resistance against penicillin in Syria [33], and (2) this study included only adults, while the WHO report included children. Amoxicillin consumption rates are usually high among children [34].

In this study, amoxicillin/clavulanic acid was the most frequently dispensed antibiotic (28.62%), followed by clarithromycin (21.87%) and cefixime (13.05%). The dispensing rates of these three broad-spectrum antibiotics account for over 50% of the total OAD in this study. This may again be linked to an increased resistance to narrow-spectrum antibiotics. Šahman-Zaimović et al. found that, in cases of high resistance to amoxicillin, amoxicillin/clavulanic acid is recommended [35]. The broad-spectrum antibiotic dispensing rates in this study are high. Further research is required, studies to determine whether the prescribing pattern aligns with the antimicrobial prescribing guidelines.

A statistically significant difference was observed in OAD rates between female and male patients. OAD was higher among female patients compared to male patients. Many studies from different parts of the world showed higher consumption or prescription rates among females than males [36–39].

The variation in OAD rates between the different age groups was statistically significant. A difference was observed in the patterns of OAD among the different age groups. The age variations in the patterns of OAD could be explained by the different infection types across the age groups. Several studies have shown variations in these patterns and a high prevalence of antibiotic use among elderly patients [37,40,41]. The adjusted OAD DID rates for age were lower among the patients aged over 60 years compared to younger patients. The reason for this result is uncertain, but it might be related to the conflict situation where younger people are most likely to be involved in the conflict and are more exposed to conflict-related injuries.

Considering the number of dispensed antibiotic packages, 15% of the OADs in this study were for parenteral administration, whereas according to the DID of the dispensed antibiotics, 1.4% were for parenteral administration. The variation in the proportion may be explained by the fact that a package of oral antibiotics has, on average, 9.02 DDDs, while parenteral antibiotic packages have, on average, 0.72 DDDs. Some physicians and patients still believe that parenteral antibiotics are more effective than oral ones [42,43]. Ceftriaxone was the most dispensed parenteral antibiotic (34.27%), followed by ceftriaxone and sulbactam (31.32%). Other studies have shown that ceftriaxone is the most common parenteral antibiotic in outpatient settings [44,45]. Ceftriaxone has a long half-life and requires one dose per day. As such, physicians and patients prefer ceftriaxone in outpatient settings [46].

The high proportion of broad-spectrum parenteral antibiotics in this study might, however, lead to more antibacterial resistance. The WHO does not recommend the use of the fixed-dose ceftriaxone and sulbactam combination on the grounds that it is not evidence-based nor recommended in high-quality international guidelines [24]. This presents evidence of the misuse of antibiotics in Syria.

The OAD of Watch antibiotics for the patients in this study was the highest (65.86% of total DID), followed by Access antibiotics (32.54%). The dispensing of Reserve antibiotics was the lowest (0.83%). The remaining antibiotics (0.76%) were not classified. Comparing these results to those from the WHO reporting the proportional consumption of antibiotics by AWaRe categorizations in three countries of the Eastern Mediterranean Region, 2015 (Iran, Jordan and Sudan), we notice that a smaller share of antibiotic consumption belongs to the Access group (32.54% in this study), while >53.8% of the antibiotics were in the Access group in Iran and 65.3% Sudan, and the share of Access was lower in Jordan (30.5%), with a larger share to the Watch group (65.86% vs. 45.0% in Iran, 17.1% in Sudan and 59.0% in Jordan), as well as to the Reserve group (0.83% vs. 0.1% in Jordan, while this was not reported in Iran or Sudan). The data in that study, unlike our study, were not limited to OAD data but included sales data and inpatient data [31]. This may show different proportions across the three groups. This result places Syria in one of worst positions in terms of the quality measures of the AWaRe classification system.

The dispensing data included seven fixed-dose antibiotic combinations. These accounted for 29.64% of the total OAD. Three of these fixed-dose combinations were listed in the Access group, and the remaining four combinations were not included in the AWaRe classification system (Table 4). These four combinations accounted for 0.82% of the total OAD. The WHO does not recommend the use of these combinations in clinical practice, as the use of these four fixed-dose combinations of multiple broad-spectrum antibiotics is not evidence-based nor recommended in high-quality international guidelines [24].

Table 4. Dispensed outpatient antibiotic combination rates among adults with health insurance in Syria classified by AWaRe categories and expressed in DID.

Combination of Antibiotics	AWaRe	DID	Proportion of the Total DID of Antibiotic Combinations
Amoxicillin + clavulanic Acid	Access	5.76	96.51%
Ceftriaxone + Sulbactam	Not Recommended	0.09	1.47%
Amoxicillin + Flucloxacillin	Not Recommended	0.06	1.08%
Sulfamethoxazole + Trimethoprim	Access	0.04	0.7%
Spiramycin + Metronidazole	Not Recommended	0.01	0.2%
Ampicillin + Cloxacillin	Not Recommended	0.002	0.04%
Ampicillin + Sulbactam	Access	0.0001	0.002%
Total		5.96	100%

We noticed in the dispensing data that some beneficiaries have dispensed antibiotics in more than one governorate. Adjusting the OAD rates according to governorates by calculating the number of DDDs per 1000 inhabitants (of each governorate) per day can be misleading. Therefore, we decided to adjust the OAD rates according to governorates by calculating the number of DDDs per 1000 OAD events per day. We do not have a certain explanation for the regional variations in the adjusted OAD rates and patterns. The adjusted OAD rates were the highest in Idlib, Quneitra and Deer el-Zour. Major parts of Idlib and Deer el-Zour were out of the Syrian government's control and were affected by the armed conflict during the study period. While the major parts of the three governorates with the lowest adjusted OAD rates (Al-Suwayda, Lattakia and Tartous) were under the Syrian government's control and less affected by the conflict [47]. The variations of the adjusted OAD rates might be related to the conflict situation in Syria.

Limitations and Strengths

This study included OAD for insured people in parts of Syria that are controlled by the Syrian government. The number of insured people in governorates such as Homs and Hamah was significantly higher than the number of insured people in the governorates of Idlib and Deer el-Zour, because large parts of these governorates are beyond the Syrian government's control. The number of people with health insurance in each governorate included in our study does not correspond to the actual population numbers and represents a limitation in terms of our ability to extrapolate our findings to the entire population. The results of this study could be possibly generalized for adults in parts of Syria that are controlled by the Syrian government and who belong to the middle-income class. The regional variations of dispensed antibiotics in this study can be related to many factors—for example, the uneven distribution of health and medical services across geographical regions [11] and the conflict situation that rendered services damaged or unavailable [48]. The conflict situation in Syria posed a challenge to mapping the parts of Syria that were under the control of the Syrian government during the study period. Further studies are required to cover the areas of Syria that are beyond the control of the Syrian government. The data did not include antituberculosis agents. The reported prevalence of tuberculosis in Syria is low (19 per 100,000 inhabitants in 2017) [49].

The data did not include the OAD that were prescribed to treat certain diseases that were excluded from health insurance coverage in Syria. The treatment for sexually transmitted diseases (STDs) or dental conditions were not covered by health insurance [50]. This raises the question of the appropriateness of policies regulating access to medicines, particularly antibiotics. We cannot claim that our study's results represent either the OAD or the total consumption or prescription of antibiotics across the entire population. To represent Syria's total antibiotic consumption, further data that includes pharmacy sales data, inpatient data, antibiotic consumption data for children and people without health insurance in regions under and outside the Syrian government's control are required.

The limited possibilities of aggregating or accessing data on antibiotics usage in Syria is a major challenge in conducting a study that aims to be representative of the entire population. This study represents a pioneering step toward the complete picture of antibiotic dispensing in Syria. It may function as a starting point for future studies that will yield a greater understanding of the prescriptions and uses of antibiotics in Syria. A major strength of this study is its use of different indicators that are often used to describe the patterns of antibiotics usage, allowing comparisons of the results of this study with those of studies describing OAD. This study describes antibiotic dispensing patterns for a part of the population in a region that is usually underrepresented in studies on antibiotics use.

5. Conclusions

This study provides the first estimates of OAD rates and patterns of a population with health insurance represented by 81,314 adults across areas controlled by the Syrian government. We observed high rates in the OAD of broad-spectrum antibiotics and high percentages of the Watch group of the AWaRE classification. These results are concerning, as the consumption of the Watch group does significantly increase the resistance against antibiotics. Further efforts are needed to investigate the quality of antibiotic use in different settings and among different groups of Syria's population. Our study provides critical findings that may help improve health insurance policies, antibiotics prescription guidelines and stewardship programs. We therefore encourage further research that would report antibiotic dispensing or consumption patterns and rates in different settings and population groups across Syria.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2079-6382/9/9/570/s1>, Table S1: The number of patients in this study according to the sex and age groups.

Author Contributions: Conceptualization: S.A., V.J.W. and E.N.; methodology: S.A. and V.J.W.; Wirtz; software: S.A.; validation: S.A. and V.J.W.; formal analysis: S.A. and V.J.W.; data curation: S.A.; writing—original draft preparation: S.A.; writing—review and editing: S.A., V.J.W. and E.N. and supervision: V.J.W. and E.N. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval: We secured approval from the ethics commission of the University of Bayreuth, who stated that the analysis and reporting of the dispensing data in this study did not require their approval.

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RESEARCH

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Outpatient cardiovascular diseases and diabetes medicines dispensing in the population with government health insurance in Syria between 2018 and 2019: a retrospective analysis

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Abstract

Background: Low- and middle-income countries bear the highest burden of non-communicable diseases (NCDs) mortality and morbidity. Syria has undergone an epidemiological transition from infectious diseases to NCDs in the past decades. Despite the high prevalence of cardiovascular diseases (CVDs) and diabetes in Syria, little is known about medicines utilization or prescriptions for these diseases. The aims of this study are to present the patterns and rates of dispensing medicines used for CVDs and diabetes among patients with government health insurance in Syria and examine age, sex, and regional variation in the dispensing of these medicines.

Methods: Outpatient data from June 2018 to May 2019 on dispensed medicines for 81,314 adults with government health insurance were obtained. The dispensing rate was expressed as the number of defined daily doses (DDDs) per 1000 beneficiaries per day (DID). The DID is a measurement that is used in drug utilization research to control for differences or changes in population size between or within countries. The number of DIDs was adjusted according to beneficiaries' sex, age, and governorate.

Results: Beneficiaries received 302.09 DIDs of CVDs medicines and 35.66 DIDs of diabetes medicines, including 0.96 DID of insulin (2.99% of the total of diabetes medicines). CVDs and diabetes medicine dispensing rates were low during the study period and included very low rates of insulin dispensing compared to the dispensing rates of these medicines in other countries in East Mediterranean Region or in Europe. We found lower dispensing rates of CVDs medicines among female beneficiaries (249.59 DIDs) than male beneficiaries (388.80 DIDs). Similarly, the dispensing rates of diabetes medicines among female beneficiaries (29.42 DIDs) were lower than those among male beneficiaries (45.98 DIDs). In addition, there were lower rates of CVDs and diabetes medicines and very low to no dispensing of insulin in some governorates that were partly controlled by the Syrian government compared to other governorates that were completely or mostly controlled by the Syrian government.

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Conclusions: Additional efforts are needed to raise awareness about the prevention and management of CVDs and diabetes especially among females in Syria and consider cultural issues that might influence access to healthcare services. There is a crucial need to address the political and geographical challenges caused by the conflict which have limited access to CVDs and diabetes medicines in some regions in Syria.

Keywords: Non-communicable disease, Cardiovascular disease, Diabetes, Medicine, Insulin, Dispensing data, Demography, Syria, Conflict

Background

Non-communicable diseases (NCDs) account for 71% of all deaths globally. Seven NCDs were in the top 10 causes of death in 2019 where cardiovascular diseases (CVDs) and diabetes are listed among the four leading causes of death globally [1, 2]. Low- and middle-income countries (LMICs) bear the highest burden of NCDs mortality and morbidity [3]. In particular, CVDs and diabetes are underdiagnosed and undertreated in LMICs and result in considerable morbidity and mortality [4]. In 2019, 463 million people were living with diabetes worldwide, with approximately 80% of those with the disease living in LMICs [5]. Similarly, over 75% of deaths caused by CVDs in 2019 occurred in LMICs [6]. It is estimated that this disease burden will continue to rise and cause financial burdens on health systems and households, particularly in LMICs [3].

Syria has undergone an epidemiological transition from infectious diseases to NCDs in the past decades. Before the onset of the conflict in 2011, NCDs (mainly CVDs, cancer, and diabetes) accounted for 77% of total mortality in the country [7, 8], with CVDs estimated to account for 25% of all deaths in 2016 in Syria [9]. Since 1980, the prevalence of diabetes in Syria has nearly tripled, to reach a total of 11.9% in 2016 [10]. During periods of conflict, people with chronic diseases such as diabetes face numerous challenges, including inadequate access to medicines and testing supplies, and food insecurity [11].

Syria is divided into 14 administrative regions (governorates) and has a population of 17,500,657 [12, 13]. The year 2021 marks the tenth anniversary of the conflict in Syria. The conflict has resulted in one of the largest humanitarian crises in the world, with 6.6 million refugees worldwide, of whom 5.6 million are hosted in nearby countries, 6.7 million internally displaced persons, and 13.4 million people in need of humanitarian and protective assistance within the country [14, 15]. Approximately 70% of health workers have fled Syria since the start of the conflict. Furthermore, nearly 600 attacks on healthcare facilities have led to approximately 50% of them being damaged or destroyed [16]. Healthcare during humanitarian crises have typically focused on infectious diseases and other acute conditions, with lower priority given to chronic diseases. However,

chronic conditions such as CVDs and diabetes are now receiving more attention as many humanitarian crises are no longer of short duration [11].

Healthcare in Syria is mainly financed by public funds, although, the costs of outpatient consultations and medicines are commonly covered by out-of-pocket expenditures [17]. There is no national health insurance that covers all inhabitants in the country. However, individuals working in public organizations, some ministries, and in professional associations are provided with health insurance [18]. This includes employees who occupy a variety of positions such as public school teachers, administrative staff, and janitors. A total of 841,852 individuals were covered by health insurance in Syria in 2019, with approximately 80% of the insured employed by the government [19]. The diagnoses and treatment of CVDs and diabetes are covered by government health insurance, however, the treatment costs of some chronic conditions such as Alzheimer's or Parkinson's are not. Moreover, health insurance does not cover the costs for the treatment of psychiatric illnesses or sexually transmitted diseases [20].

The prevention and control of CVDs and diabetes usually require lifestyle changes. However, pharmacological therapies are also key elements for their management [21, 22]. Diabetes, in particular, is a costly disease to manage in LMICs [23]. Globally, one in two people with type-2 diabetes have no access to the insulin they need; however, in some LMICs, this proportion is only one in six to seven patients have access to insulin [24]. The survival of 400,000 diabetic patients in Syria depends on access to insulin. Thus, due to limited supplies, approximately 60% of insulin-dependent patients are at risk [10, 11, 25]. Even when medicines are available during humanitarian crises and in conflict regions, their distribution can be challenging due to political and geographical barriers [11].

Previous studies have reported different utilization patterns for CVDs and diabetes medicines in different countries, including Iran, India, and many European countries [26, 27]. Furthermore, different patterns and higher rates of CVDs medicines prescription have been identified among males compared to females [28]. Despite the high prevalence of CVDs and diabetes in Syria, little is known about medicines utilization or

prescriptions for these diseases [29]. Therefore, the aims of this study are to: 1) present the patterns and rates of dispensing medicines used for CVDs and diabetes among patients with government health insurance in Syria, and 2) examine age, sex, and regional variation in the dispensing of these medicines.

Methods

Data sources and patients

This study is based on outpatient medicines dispensing data from 13 out of 14 Syrian governorates. These data were only from the parts of the country under the Syrian government's control. The government health insurance system was not functioning in the parts of the country that were out of the Syrian government's control. Therefore, no data were available from the Ar-Raqqa governorate or some parts of other governorates, which were not under the control of the Syrian government. We used health insurance data from 81,314 adult beneficiaries employed by the Syrian government and covered by the health insurance scheme, members of professional organizations, and university students who were privately insured. The data covered a 12-month period starting from June 2018. Outpatient dispensing data included the following information regarding each dispensed medicine: product name, dose, pharmaceutical form, and administration route. Additional information shared by the health insurance company were used to identify the international non-proprietary name of each product. In addition, the data included information on the age and sex of each beneficiary, the dispensing date, prescription number, an identical number for each patient, and the name of the governorate where the medicine was dispensed.

Data analysis

We used the World Health Organization's (WHO's) anatomical therapeutic chemical classification/defined daily dose (ATC/DDD) (version 2020) methodology to analyse the dispensed medicines. The defined daily dose (DDD) is "the assumed average maintenance dose per day for a drug used for its main indication in adults" [30]. The rate of dispensed medicine was expressed as the DDD per 1000 inhabitants (this corresponds to 1000 beneficiaries in our study) per day (DID). The DID is a measurement that is used in drug utilization research to control for differences or changes in population size between or within countries [31]. Medicines have been grouped using the ATC classification. In this study, CVD medicines included those from ATC groups C (cardiovascular system) and B01 (antithrombotic agents). Diabetes medicines included medicines from ATC group A10 (drugs used for diabetes). Medicine dispensing is presented according to the anatomical main group

(ATC1), the therapeutic subgroup (ATC2), the pharmacological subgroup (ATC3), and the chemical substance subgroup (ATC5). We used the drug utilization 90% (DU90%) methodology to reflect the number of medicines that accounted for 90% of the dispensing rates for CVDs and diabetes medicines [32]. The number of DIDs was adjusted according to patient sex and age using the number of beneficiaries in each sex and age group which was available through the dispensing data we used in this study.

To adjust the number of DIDs according to regions or states, studies from Germany and Hungary have calculated the number of DDDs per 1000 inhabitants of each region per day [33, 34]. This analysis assumed that in these stable and high-income countries, the inhabitants of any region or state would have access to the medicines in that same region or state where they live. In Syria, the disruption of healthcare in some parts of the country due to the conflict has forced patients to flee their homes to other parts of the country to access better healthcare [35]. Our data showed that some beneficiaries had medicines for CVDs and diabetes dispensed in more than one governorate. Therefore, adjusting CVDs and diabetes medicines dispensing rates according to governorates by calculating the number of DDDs per 1000 beneficiaries (of each governorate) per day can be misleading. The CVDs and diabetes medicines dispensing rates were adjusted according to governorates by calculating the number of DDDs per 1000 medicine dispensing events per day (DDED) [36]. The medicine dispensing events here refers to the dispensing of CVDs or diabetes medicines.

Statistical analysis

The dispensing data in this study displayed evidence of a skewed distribution of the outcome variable "rates of dispensed medicines". Therefore, statistical significance differences between the variables of interest were assessed using nonparametric testing. The Mann-Whitney U test was used to analyze differences between the medians of the medicine dispensing rates between females and males. The Kruskal-Wallis nonparametric ANOVA was used to examine differences between the different age groups and governorates in regard to medicine dispensing rates. We considered a *p*-value of 0.05 as a cut-off value for significance in all the tests. Analyses were conducted using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY, USA).

Results

This study used the outpatient medicine dispensing data of 81,314 adult beneficiaries who were at least 18 years of age and covered by government health insurance in Syria. The median age of the beneficiaries was 47 years

(interquartile range: 37–56), and 50,673 beneficiaries (62.28%) were female and 30,671 (37.72%) were male. Table 1 lists the characteristics of the study population. The median age of the beneficiaries in Damascus, Aleppo, and Quneitra were the lowest, while the highest median age occurred in Tartous, Latakia, and Al-Suwayda (Additional file 1).

Of the total number of beneficiaries, 46,281 (56.92%) received at least one medicine in the 12-month period from June 2018 to May 2019. The total number of DIDs dispensed for these patients was 591.21 DIDs. Considering the number of DIDs, medicines in anatomical main group C (the cardiovascular system) of the ATC classification system were the most dispensed (35.78%), followed by those in group A (the alimentary tract and metabolism) (22.43%) (Additional file 2).

A total of 14,523 patients (17.84%) received 302.09 DIDs of medicines used for cardiovascular system (C) and antithrombotic agents (B01). Medicines in the ATC therapeutic subgroup B01 (antithrombotic agents) were the most dispensed medicines (90.54 DIDs) followed by C10 (lipid-modifying agents; 83.64 DIDs) and C09 (renin-angiotensin system agents; 64.48 DIDs) (Table 2).

A total of 4466 patients (5.49%) received 35.66 DIDs of diabetes medicines (medicines used in diabetes: A10). Medicines in the pharmacological subgroup A10B (blood glucose lowering drugs, excluding insulin; 34.70 DIDs) were the most dispensed among diabetes medicines, while 0.96 DID of the A10A group (insulin and analogues) were dispensed for diabetes patients (Table 3).

Acetylsalicylic acid was the most dispensed CVDs medicine (60.84 DIDs) followed by rosuvastatin (47.56 DIDs) and clopidogrel (23.03 DIDs). Thirty medicines accounted for 272.92 DIDs, which were 90% of the total DIDs of the dispensed CVDs medicines. Metformin was the most dispensed diabetes medicine (8.29 DIDs) followed by gliclazide (7.44 DIDs) and the fixed dose combination of metformin and sulfonylureas (6.82 DIDs). Eight medicines accounted for 32.76 DIDs, which were 91.86% of the total DIDs of the dispensed diabetes medicines (Additional file 3).

Table 1 Characteristics of the study population by age and sex

Age group	Female		Male		Total	
	n	%	n	%	n	%
18–29	5257	6.46	2861	3.52	8118	9.98
30–39	13,180	16.21	4603	5.66	17,783	21.87
40–49	12,372	15.22	8299	10.21	20,671	25.43
50–59	13,189	16.22	8741	10.75	21,930	26.97
60–69	5733	7.05	4311	5.30	10,044	12.35
70≤	912	1.12	1856	2.28	2768	3.40
Total	50,643	62.28	30,671	37.72	81,314	100

Of the 4466 patients who received diabetes medicines, 117 (2.62%) received 0.96 DID of insulin and analogues. Approximately 30% of the dispensed insulins were insulin analogues. Human insulin (intermediate- or long-acting combined with fast-acting insulin) was the most dispensed (0.55 DIDs) followed by insulin aspart (0.18 DIDs) and fast-acting human insulin (0.9 DIDs) (Table 3).

We found that 16.12% (8384) of female beneficiaries and 19.66% (6141) of male beneficiaries received outpatient CVDs medicines. The adjusted DID rates of CVDs medicines were higher among male patients (388.80 DIDs) than female patients (249.59 DIDs) and this difference was statistically significant ($p < 0.001$). Among both females and males, the CVDs medicines in the ATC therapeutic subgroup B01 (antithrombotic agents) were the most dispensed followed by C10 (lipid-modifying agents) and C09 (renin-angiotensin system agents) (Fig. 1). We found that 4.91% (2489) of the female beneficiaries and 6.45% (1977) of the male beneficiaries received outpatient diabetes medicines. The adjusted DID rates of diabetes medicines were higher among males (45.98 DIDs) than females (29.42 DIDs) and this difference was statistically significant ($p < 0.001$). The adjusted DID rates for insulins were also higher among male patients in comparison to females (1.14 DIDs and 0.85 DIDs, respectively).

For beneficiaries in the age group 18–29, 3.76% received CVDs medicines. The proportion of patients who received CVDs medicines increased with age and was 50.53% in the 70 ≤ age group. The adjusted DID rates of CVDs medicines were the lowest in the 18–29 age group (1.80 DIDs) and increased to 1229.04 DIDs in the 70 ≤ age group. This difference was statistically significant ($p < 0.001$). The CVDs medicines in the ATC therapeutic subgroup B01 (antithrombotic agents) were the most dispensed CVDs medicines followed by C10 (lipid-modifying agents) and C09 (renin-angiotensin system agents) in all age groups except in the 30–39 age group where the ATC therapeutic subgroup C10 (lipid-modified agents) were the most dispensed, followed by B01 (antithrombotic agents) (Fig. 2).

Of the beneficiaries in the age group 18–29, 0.58% received diabetes medicines. The proportion of patients who received diabetes medicines increased with age to 21.46% in the 70 ≤ age group. The adjusted DID rates of diabetes medicines were the lowest among patients in the 18–29 age group (0.28 DIDs) and increased to 131.34 DIDs in the 70 ≤ age group (Fig. 3). This difference was statistically significant ($p < 0.001$).

We found a statistically significant difference ($p < 0.001$) in CVDs medicine dispensing rates between Syria's different governorates. According to the number of DDEDs in each governorate, the Damascus countryside

Table 2 Outpatient dispensing rates of CVDs medicines according to the therapeutic subgroup (ATC2)

	Therapeutic subgroup (ATC2)	DID ^a		patients	
		n	%	n	%
Cardiovascular diseases medicine	Antithrombotic agents (B01)	90.54	15.31	9433	11.60
	Lipid-modifying agents (C10)	83.64	14.15	8765	10.78
	Renin-angiotensin system agents (C09)	64.48	10.91	8377	10.30
	Beta-blocking agents (C07)	30.48	5.16	6543	8.05
	Calcium-channel blockers (C08)	14.35	2.43	2031	2.48
	Cardiac therapy (C01)	9.26	1.57	1438	1.77
	Diuretics (C03)	8.12	1.37	1336	1.64
	Antihypertensives (C02)	1.00	0.17	334	0.41
	Peripheral vasodilators (C04)	0.18	0.03	230	0.28
	Vasoprotectives (C05)	0.04	0.01	2441	3.00
Total		302.09	51.11	14,532 ^b	17.84 ^b

^aOutpatient medicines dispensing according to the therapeutic subgroup (ATC2) is expressed as the number of defined daily doses (DDDs) per 1000 people per day (DID)

^bSome patients dispensed different CVDs medicines. To avoid counting these patients more than once, we considered the identical number for each patient while calculating the total number and percentage of patients

(1655.03 DDED), Latakia (1203.21 DDEDs), and Tartous (998.37 DDEDs) had the highest CVDs medicine dispensing rates, while Deer el-Zour (39.38 DDED), Idlib (45.71 DDEDs), and Quneitra (120.69 DDEDs) had the lowest CVDs medicine dispensing rates (Fig. 4).

In terms of diabetes medicine dispensing rates, the difference between Syria's different governorates was statistically significant ($p < 0.001$). The Damascus countryside (205.23 DDEDs), Latakia (147.75 DDEDs), and Tartous (127.11 DDEDs) had the highest diabetes medicine dispensing rates, while Idlib (1.01 DDEDs), Deer el-Zour (4.07 DDEDs) and Quneitra (15.61 DDEDs) had the

lowest diabetes medicine dispensing rates (Fig. 5). The highest insulin dispensing rates were recorded in the Damascus countryside (14.32 DDEDs), Latakia (6.85 DDEDs), and Al-Suwayda (6.74 DDEDs). The insurance data did not record insulin dispensing in the governorates of Al-Hasakah, Idlib, Deer el-Zour, or Daraa (Additional file 4).

Discussion

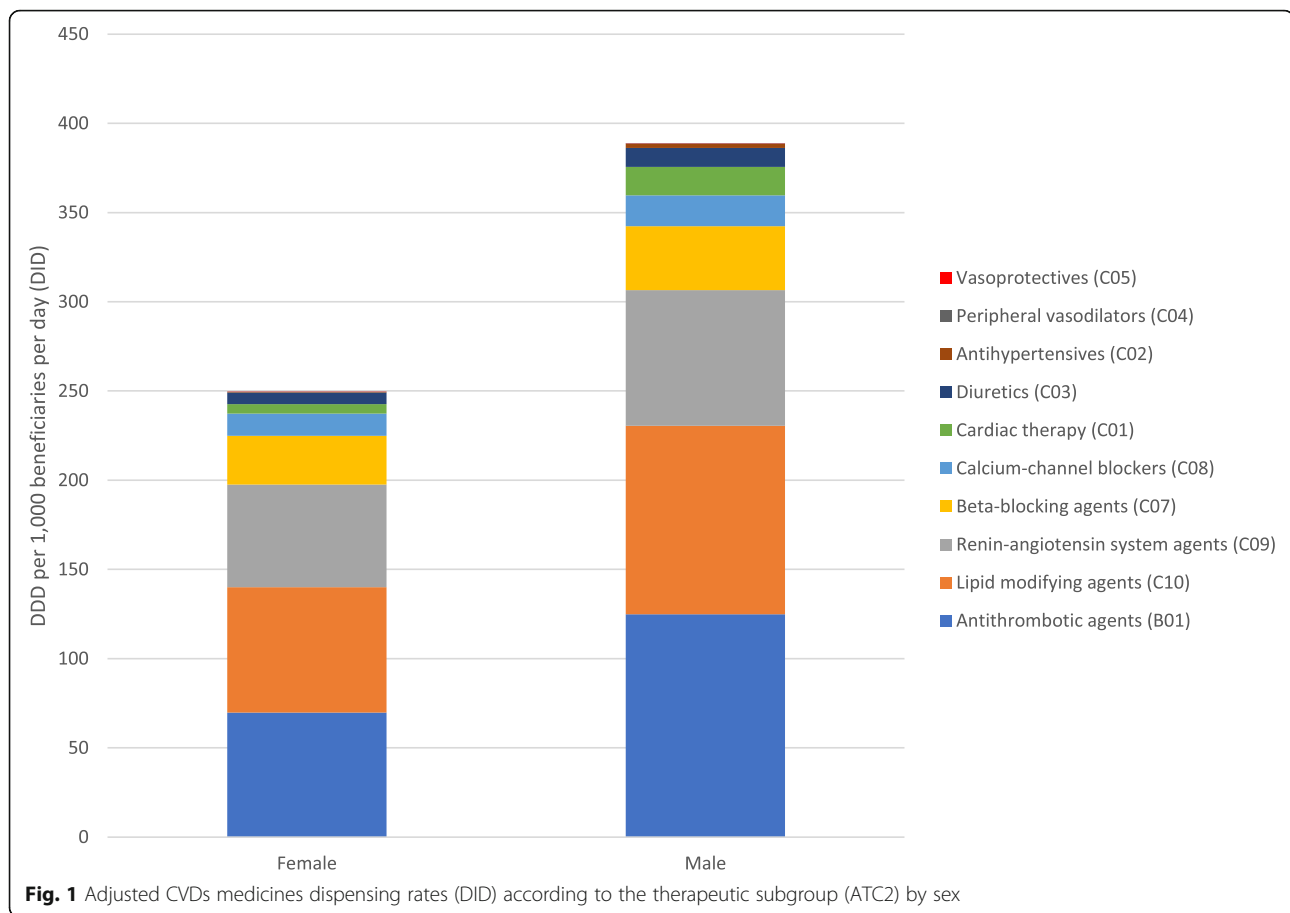
To the best of our knowledge, this is the first study to report CVDs and diabetes medicine dispensing at the population level in Syria using health insurance data

Table 3 Outpatient dispensing rates of diabetes medicines according to the pharmacological subgroup (ATC3) including insulin (ATC5)

Therapeutic subgroup (ATC3)	DID ^a		Patients	
	n	%	n	%
Insulin and analogues (A10A)	0.96	0.16	117	0.14
Blood glucose lowering drugs excluding insulins (A10B)	34.70	5.87	4413	5.43
Total	35.66	6.03	4466 ^b	5.49 ^b
Medicine (ATC5)	DID ^a		Patients	
	n	%	n	%
Insulin (human) intermediate- or long-acting combined with fast-acting (A10AD01)	0.55	0.09	67	0.08
Insulin aspart (A10AD05)	0.18	0.03	25	0.03
Insulin (human) fast acting (A10AB01)	0.09	0.02	10	0.01
Insulin lispro (A10AD04)	0.08	0.01	12	0.01
Insulin glargine (A10AE04)	0.04	0.01	9	0.01
Insulin (human) intermediate acting (A10AC01)	0.02	0.004	4	0.005
Total	0.96	0.16	117 ^b	0.14 ^b

^aDispensing rates of diabetes medicines including insulin are expressed as the number of defined daily doses per 1000 people per day (DID)

^bSome patients dispensed different diabetes medicines. To avoid counting these patients more than once, we considered the identical number for each patient while calculating the total number and percentage of patients

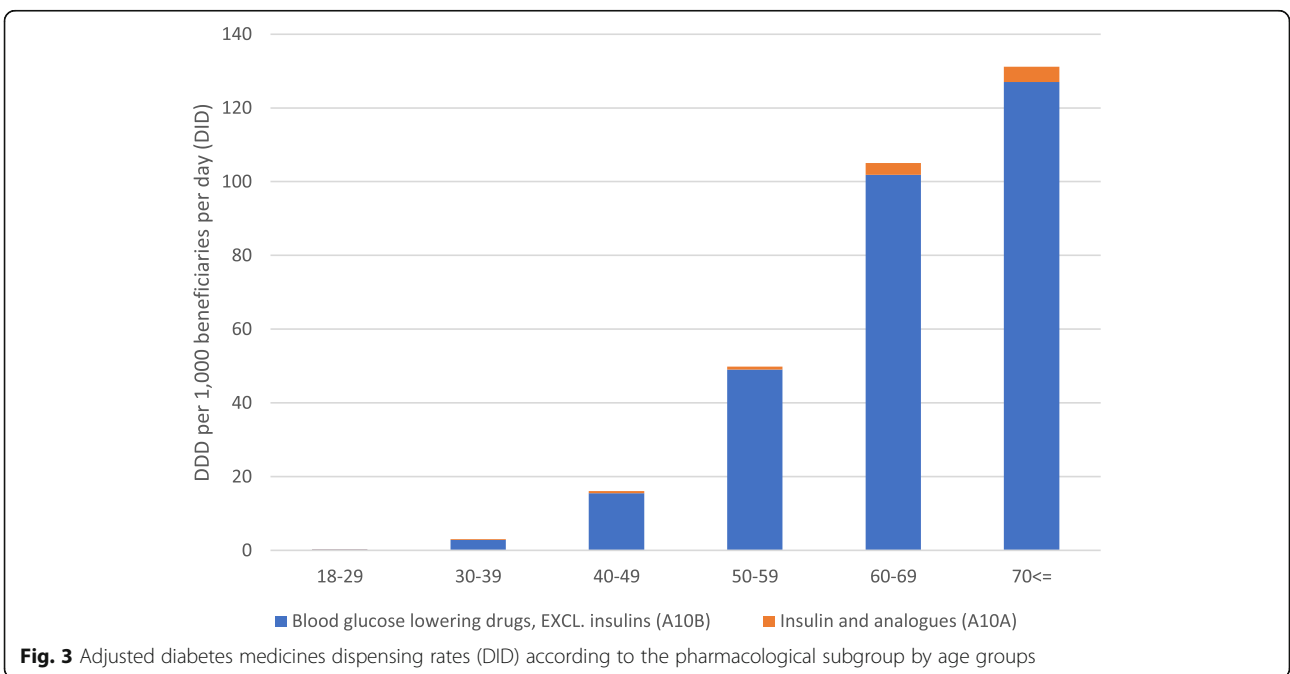
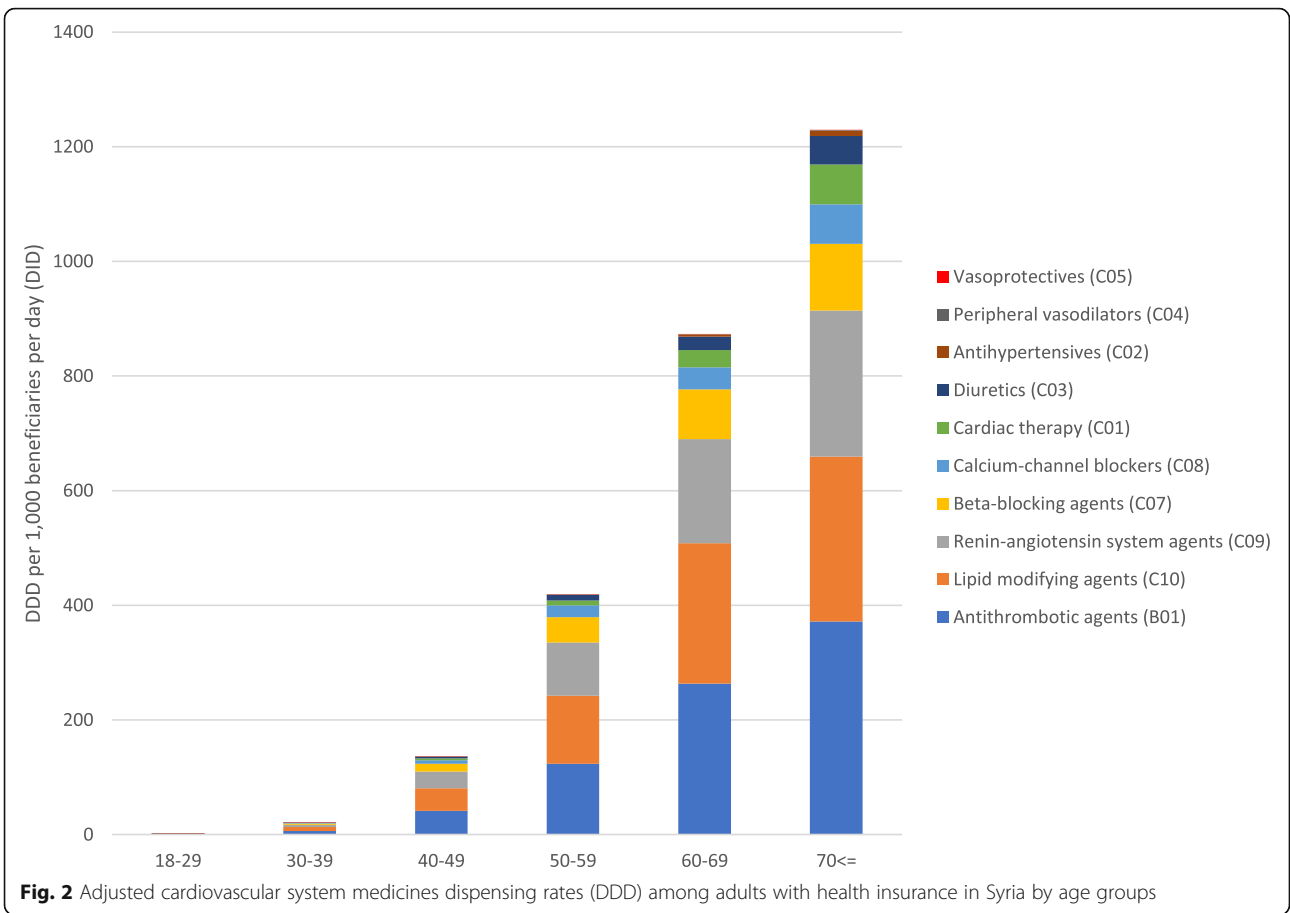


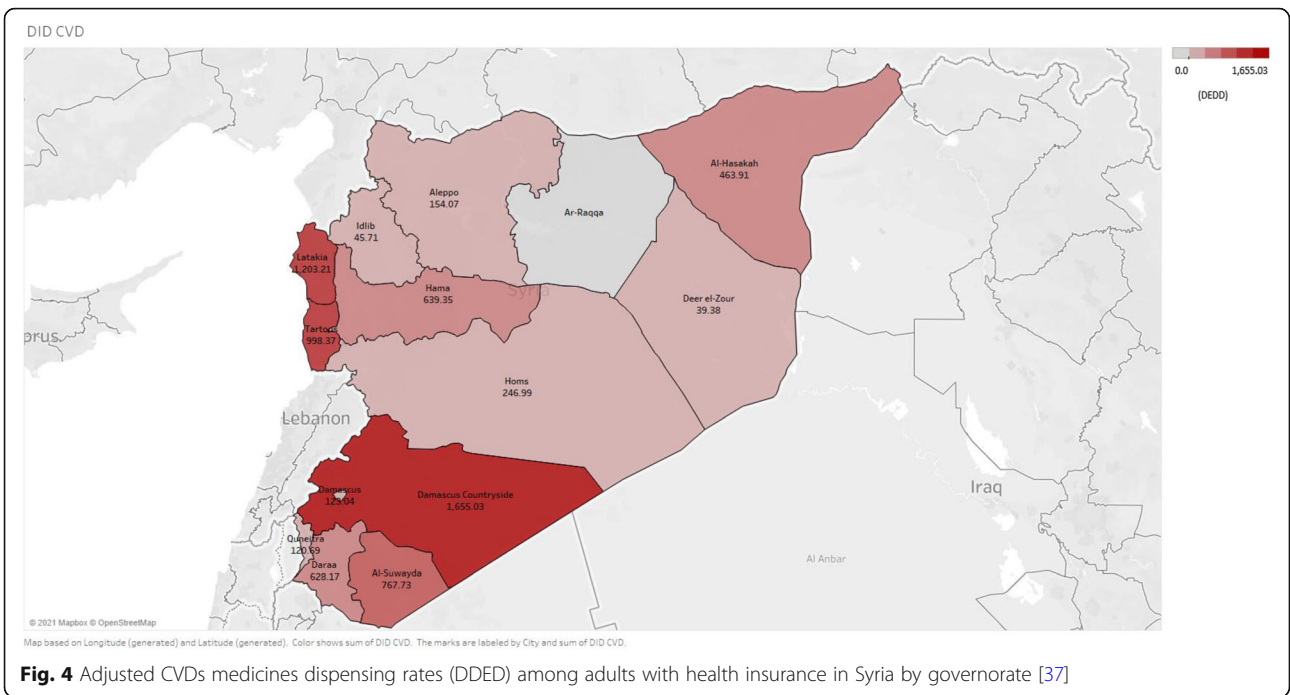
from a large sample (81,314 beneficiaries) over a 12-month period. This study contributes to our knowledge regarding treatments for two common NCDs in Syria: CVDs and diabetes. Our analysis yielded three key findings: 1) CVDs and diabetes medicine dispensing rates were low during the study period and included very low rates of insulin dispensing; 2) there were lower dispensing rates of CVDs and diabetes medicines among female beneficiaries compared to male beneficiaries; and 3) there were higher rates of CVDs and diabetes medicines dispensed in governorates that were completely or mostly controlled by the government and very low to no dispensing of insulin in some governorates that were partly controlled by the Syrian government.

The rates for dispensing cardiovascular system medicines (C) were the highest in comparison to the other medicine groups. This can be explained by the high rate of CVDs in Syria [38]. CVDs medicine dispensing rates in our study were, however, low compared to many other countries. A study from Australia reported higher rates of dispensed CVDs medicines (566.00 DIDs) [39], and a study from Serbia reported higher dispensing rates for some antihypertensives (283 DIDs) compared to the dispensing rates of antihypertensives in our study [40].

These differences in medicine use between countries may be the result of differences in the age and sex distribution of the populations, differences in the prevalence of high blood pressure and cholesterol, and variation in clinical practices [41]. Other reasons for the low dispensing rates of CVDs medicines found in this study could be associated with the ongoing conflict in Syria. Access to medicines, including CVDs medicines, can be affected by several barriers, including travel bans and checkpoints during conflict [42].

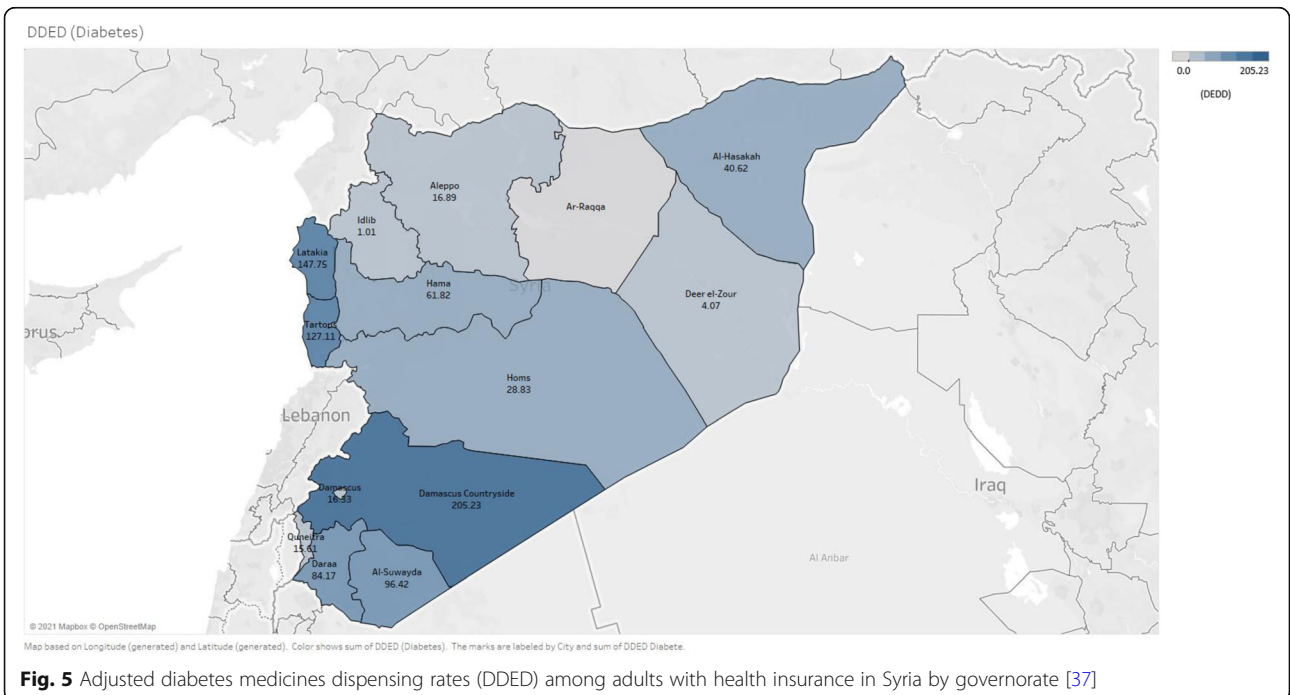
The dispensing rate of diabetes medicines in Syria was quite low compared to those in other countries. A study that reported on the consumption of antidiabetic medicine in the 28 countries of the Organization for Economic Co-operation and Development (OECD) found that the average rate of diabetes medicine consumption was 68 DIDs, which is nearly double the rate found in our study. Similarly, in neighbouring Turkey the consumption rate of diabetes medicine is 73 DIDs, which is more than double the rate we found in our study [43]. Another study reported that the rate of diabetic medicine consumption in Iran in 2012 was also low in comparison to other countries (33.54 DIDs) [26]. However, this rate may have increased in the years 2018–2019 to





exceed the rate of diabetes medicine consumption in our study, as the authors of that report indicated an ongoing increase in diabetes medicine rates with time in Iran. The low dispensing rates of diabetetic medicine that we found could be related to a potentially high number of undiagnosed diabetes in Syria. The WHO has reported that four in five undiagnosed diabetetic patients live in LMICs [44]. One study has reported that diabetes was

well controlled in only 16.7% of type-2 diabetes patients in Aleppo in 2011—before the start of the conflict [45]. Since there is an evidence on the low number of controlled diabetes cases it would be expected that there is a low rate of diabetes medicines utilization. In addition, the low dispensing rates of diabetes medicines may be explained by factors related to the conflict situation in Syria. A study conducted among a group of diabetes



patients in main public hospitals in Damascus during the Syrian crisis reported that 41.2% of the patients had stopped their medicines for at least 1 month over the course of 7 years of conflict, and 74.8% of these patients attributed stopping their therapy to the unavailability of medicines. Furthermore, approximately half of the patients had to change their medicines brand names because many pharmaceutical companies closed due to the conflict. In addition, half of the diabetic patients struggled to reach a healthcare center [46]. Moreover, food insecurity in countries affected by conflict limits the possibility of diabetes patients to adhere to recommended diets, which would present an obstacle to maintaining treatment as diabetes medicines must be taken with food [47].

Compared to the insulin dispensing rate in our study, higher rates of insulin prescriptions in other countries has been reported. For instance, a study from Albania reported a 5.64 DIDs insulin outpatient prescription rate [48], while Iran reported higher insulin consumption rates in 2012 (5.73 DIDs) [26]. A study from Portugal reported an insulin dispensing rate of 15.1 DIDs in 2014. In addition to the factors we have previously mentioned to explain the low dispensing rates of diabetes medicine, specific factors related to insulin could also explain the low rates. The limited availability of insulin due to the conflict in the country may be another factor. Approximately 60% of insulin-dependent Syrians are at risk due to limited supplies [11, 25]. Furthermore, insulin requires cold-chain transportation and the maintenance of temperatures between 2 °C and 8 °C. The storage of insulin by patients is an additional challenge as the lack of refrigeration is common due to frequent energy cuts [11]. In addition, our data may not include all of the insulin given to insulin-dependent diabetic patients, as they could have received insulin through other channels such as humanitarian organizations—the WHO is now the main supplier of insulin in Syria [25]. Poor adherence to insulin caused by injection phobia among some patients has been recorded in other studies [47]. This can also further explain the very low rates of insulin dispensing in our study.

CVDs medicine dispensing rates were significantly higher among males than females. Other studies have reported higher rates of hypertension among middle-aged females (35 to 65 years) than males in Syria and other countries of the Eastern Mediterranean region and North Africa [49]. Moreover, women of Arab ethnicity present with coronary artery disease 10 years earlier than those from Europe or East Asia [50]. Obesity, a significant risk factor of CVDs, also has a higher prevalence among females in Eastern Mediterranean region countries, including Syria, compared to males in these countries [38, 51, 52]. Cultural and religious norms, as well as

circumstances related to the conflict and lack of security, restrict women from sports and limit physical activity. These factors may also contribute to the CVDs burden among women in Syria and the region [50]. The low dispensing rates of CVDs medicines among females in our study contrasts with other studies that have reported high rates of CVDs in females in Syria. This suggests that CVDs were undertreated among females in our study population. Despite being the leading cause of death among women globally, CVDs in women are still understudied, underdiagnosed, and undertreated [53]. There is a common misperception that CVDs affect men more than women, and this may contribute to the sub-optimal treatment of CVDs among women [28]. Similar to CVDs, the dispensing rates of diabetes medicines, including insulin dispensing rates, were significantly higher among males than females; however, the WHO has reported a higher prevalence of diabetes among females in Syria than males [25]. This result indicates the undertreatment of diabetes among females in our study. Other studies have reported poorer control of type-2 diabetes among women than men [54–56]. Furthermore, the conflict situation in Syria may have contributed to women's vulnerability in comparison to men. This crisis has restricted women's movement more than men and limited their access to healthcare, including diabetic care [11, 57]. Unsurprisingly, the dispensing rates of CVDs and diabetes medicines increased with increasing age, which is due to the increasing prevalence of CVDs and diabetes with increasing age [58, 59].

There was a significant difference in the dispensing rates of CVDs and diabetes medicines between the different governorates in Syria. The Damascus countryside, Latakia, and Tartous had the highest dispensing rates for CVDs and diabetes medicines, while Idlib, Deer el-Zour, and Quneitra had the lowest rates. The major areas of the three governorates with the highest CVDs and diabetes medicines dispensing rates (Damascus countryside, Latakia, and Tartous) were under the Syrian government's control. However, while the major areas of Deer el-Zour and Idlib were out of the Syrian government's control, they were affected by the armed conflict during the study period [60]. This regional variation may be related to the conflict situation that has rendered services damaged or unavailable. There is an uneven distribution of healthcare services, including medicines, across geographical regions [61, 62]. Through internal displacement, the conflict has also contributed to regional variation in Syrian healthcare services. The disruption of healthcare in some parts of Syria has forced patients with chronic diseases, especially older individuals, to flee their homes to other parts of the country to access better healthcare [35]. Our data did not

record insulin dispensing in Al-Hasakah, Idlib, Deer el-Zour, and Daraa. Being a cold chain product, delivery of insulin in these regions may have been extremely challenging. The distribution of essential medicines, including insulin even when it was available, can be complex due to geographical and political barriers as many parts of the country, especially those remote from the regime hubs, are controlled by opposing forces to the Syrian government [11].

Strengths and limitations

The study's limitations principally arose from the data that was used, as it did not provide the diagnoses underlying the prescribed medicines. The generalizability is also limited as our data only included people with government health insurance. The majority of our study population were employed by the Syrian government. Government employees in Syria belong usually to the country's middle-income class [63]. The study did not include people living in areas of Syria that were out of government control. In particular, the number of insured people in Deer el-Zour and Idlib was significantly lower than other governorates because large areas of these regions were beyond the Syrian government's control. Further studies are necessary to reach those regions. Our data did not necessarily include all the diabetes medicines used by diabetic patients because some might receive these medicines, especially insulin, through other sources such as humanitarian organizations. Despite these limitations, our study represents an essential step towards understanding medicine use for NCDs such as CVDs and diabetes in a country plagued by an ongoing conflict since 2011. Our research also provides a picture of CVD and diabetes management in a large sample that is diverse in terms of age and sex and included data on medicine use in 13 out of 14 Syrian governorates. Finally, reporting medicine dispensing rates and patterns using ATC/DDD methodology enables the comparison of medicine dispensing at the international level [64].

Conclusions

This study presents the first estimates of CVDs and diabetes medicines dispensing rates and patterns at population level in Syria using health insurance data from a large sample (81,314 beneficiaries) over 12 months. Our study demonstrated significant difference in CVDs and diabetes medicines dispensing rates between male and female beneficiaries. This study also showed significant regional variation in CVDs and diabetes medicines dispensing with low CVDs and diabetes medicines dispensing rates and very low to no dispensing of insulin in some governorates that the Syrian government partly controlled. Additional efforts are needed to raise awareness about the prevention and management of CVDs

and diabetes, especially among females in Syria including cultural issues that might influence access to healthcare services. In addition, the growing importance of NCDs during humanitarian crises should be recognized by all healthcare providers. Humanitarian healthcare workers should be trained to handle CVDs and diabetes emergencies. There is a crucial need to address the political and geographical challenges caused by the conflict in Syria, limiting access to CVDs and diabetes medicines in some regions in Syria. It is the responsibility of the Syrian government and the other different actors across the country to ensure continuous access to healthcare services, including essential medicines, to the population in the different regions of Syria. We encourage further research that would address CVDs, and diabetes medicines use in the areas beyond the control of the Syrian government and among the groups of the population that are not covered by the government health insurance. Future research should give more attention to improving the prevention and management of NCDs during humanitarian crises.

Abbreviations

ATC: Anatomical Therapeutic Chemical Classification; CVD: Cardiovascular Disease; DDD: Defined Daily Dose; DDED: Number of Defined Daily Dose per 1000 Medicine Dispensing Events per Day; DID: Defined Daily Dose per 1000 beneficiaries per day; DU90%: Drug Utilization 90%; LMICs: Low- and Middle-Income Countries; NCD: Non-Communicable Disease; OECD: Organization for Economic Co-operation and Development; WHO: World Health Organization

Supplementary Information

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Additional file 1. Median age of beneficiaries by governorate.

Additional file 2. Outpatient medicines dispensing rates according to the anatomical main group (ATC1).

Additional file 3. DU90% of CVDs and diabetes medicines.

Additional file 4. Adjusted insulin dispensing rates (DDED) among adults with health insurance in Syria by governorate.

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Authors' contributions

Conceptualization, SA, EN and VJW; Methodology, SA, EN and VJW; Formal Analysis, SA and VJW; Data Curation, SA; Writing—Original Draft Preparation, SA; Writing—Review & Editing, SA, EN and VJW; Supervision, EN and VJW. All authors critically revised the manuscript and approved the final version.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due a request from the data provider but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Individual patients could not be identified through the information in the dispensing data used in this study. The ethics committee of the University of Bayreuth stated that the analysis and reporting of the dispensing data in this study did not require their approval. This study is an anonymized, secondary data analysis study; no consent to participate was necessary.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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