Antibiotic Prescriptions Before, During and after the Corona Pandemic in Schleswig-Holstein with Prescription Data from 2017 till 2023

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Abstract: The ongoing COVID-19 pandemic threatens the health of humans, causes great economic losses and may disturb the stability of the societies and is a major challenge for physicians, politicians, scientists and many other groups. The article focuses on patients with antibiotic prescriptions and considers their risks in comparison to all patients. Time series are analyzed starting from the pre-Corona period till today. Mathematical analysis can be used to understand aspects of the dynamics of epidemics and to improve strategies, i. e. regarding effects of antibiotic stewardship programs or reaction to drug availability constraints.

1 INTRODUCTION

The Covid-19 pandemic is a major challenge for physicians, politicians, scientists and many other groups. Models help in the discussion of possible scenarios, allow to monitor the consequences of interventions and to generate more background knowledge for the refinement of policy impact research, cf. (Chinazzi et al., 2020), (Rosenbaum, 2020), (Pan et al., 2020), (Behrens et al., 2020), (Tang et al., 2020). The outbreak of the COVID-19 pandemic in March 2020 led to significant changes in the burden of disease and in the medication prescription patterns in Germany. To turn up at work despite flu symptoms, even though it would be appropriate to report sick, used to be daily occurrence, especially among service employees. By contrast during the pandemic, this had been viewed much more critically due to the general risk of infection. Persons showing flu-like symptoms were suspected as possible candidates for SARS-CoV-2 virus infection. In most cases, they were requested by the employer to stay at home to prevent further spread of the illness. This effect as well as the public pandemic-related infection protection measures starting in spring 2020 led to fewer respiratory infections and therefore fewer cases of incapacity for work due to this diseases. The problem of excessive use of reserve antibiotics has been discussed for a long time in the statutory health insurance and changes during the pandemic are therefore also relevant. Another problem are the delivery bottlenecks, especially for antibiotics for children.

Nationwide antibiotic stewardship initiatives aim to ban the inappropriately excessive use of antibiotics and of reserve antibiotics for flu-like symptoms, so changes during the pandemic are relevant to monitor. Another relevant problem are pandemic-related delivery bottlenecks, regarding unit dosage forms especially made for children, respectively.

2 MATERIAL AND METHODS

We analyse prescription and diagnostic data of the most northern federal state of Germany (Schleswig-Holstein) from quarters 1/2017 till 2/2023. The analysis relates to patients, quarters and physicians. Counting a patient as often as pairs of quarters and physicians appear results in 153 million drug prescription data records.

The C-related programming language awk is used for the computations. The visualization is performed using Mathematica by Wolfram Research and Microsoft Excel.

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For the prescription analysis, the International Anatomical Therapeutic Chemical classification system (ATC) with specifications provided by the German National Institute for Drugs and Medical Devices (BfArM) is used with ATC code J01 as identifier for antibiotic drugs, cf. (Fricke et al., 2009).

3 RESULTS

Comparing the total number of antibiotic prescriptions per quarter in the period between the first quarter of 2017 and the second quarter of 2023, there is both a seasonal trend and a decrease per year in the pre-Corona period from 2017 to 2020, cf . (Bornemann and Tillmann, 2022). The decisive drop in the number of prescriptions is observed following the pandemic breakout in the second quarter of 2020 and continues until the second quarter of 2021. The number of prescriptions than rises again to reach the highest level during the observation period in the first quarter of 2023, cf. (Kolbe, 2021), (Tarazi et al., 2021), (Patel et al., 2021), (Olsen et al., 2020) and (Smits et al., 2019). The reductions in the pre-Corona period were overcompensated by the development after 2021, suggesting that increased health risks are met in the period after the Corona pandemic. The time series is shown in Figure 1.

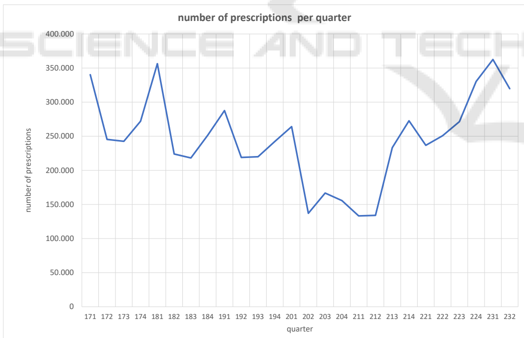

Figure 1: Time series of antibiotic prescriptions.

In order to consider the age distribution for all and for antibiotic drugs in 2019, that means that the area under the curve in Figure 2 is normed. The age distribution in 2020 is nearly the same, the differences in the prescription numbers are almost completely reduced by the normalization. Because aspects of polypharmacy are included, it differs from the age distribution of the related patients.

In contrast to all prescriptions, there is initially a local maximum at the age of two to four years for antibiotic prescriptions. This is followed by a relative minimum at the age of 13 for both observations.

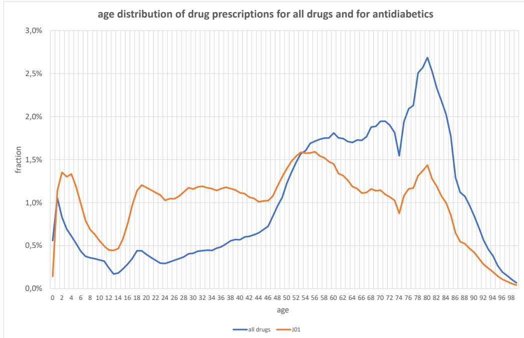

Figure 2: Age distribution with respect to all drugs and for antibiotic drugs.

Again, there is another relative prescription maximum for both observations at the age of 19 when people start to assume working or studying. Considering antibiotic prescriptions, the absolute maximum is reached between the ages of 53 and 56, while the overall number of prescriptions continues to rise. At the age of 54 years, there is an intersection of the normalized curves. There is a narrow local minimum at the end of the war in 1945, which corresponds to the age of 74 in 2019. On one hand, the curves are characterized by the slowly emerging baby boomer generation, on the other by the increased probability of illness and death of older people. Both the choice of antibiotics and the prescriptions as a whole peak at an age of 80 (relatively for antibiotics, absolutely for all prescriptions). Our age-related considerations of antibiotic prescriptions in the pre-pandemic period and during the pandemic are concordant with the findings in (European Centre for Disease Prevention and Control, 2020), (Holstiege et al., 2019), (Augustin et al., 2015), (Koller et al., 2013) and (Gillies et al., 2022).

The age spectrum of antibiotic prescriptions in the pre-Corona year 2019 and the year of the outbreak in 2020 barely differs, with a certain shift towards older ages, Figure 3. This accounts for the generally higher risk, but the insignificance of this effect is noteworthy.

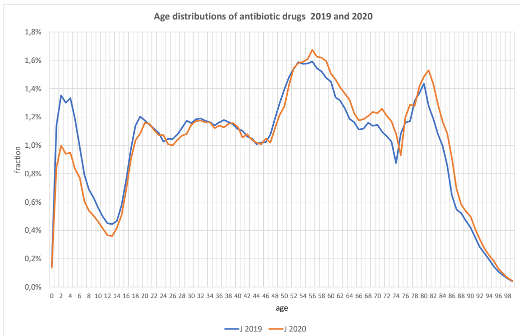

Figure 3: Age distributions for antibiotic drugs 2019 and 2020.

We compare the prescription of antibiotics between 2019 and 2020 at different ATC levels and start with the ATC 4 level, cf. Table 1.

Table 1: ATC 4 prescriptions 2019 and 2020.

ATC 4	nr. 2019	nr. 2020	diff.rel.	drug group
J01C	301,672	218,899	-27.4 %	beta-lactam antibacterials, penicillins
J01D	205,392	151,232	-26.4 %	other beta-lactam antibacterials
J01F	163,670	100,860	-38.4 %	macrolides, lincosamides and streptogramins
J01X	97,910	92,920	-5.1 %	other antibacterials
J01E	72,058	58,767	-18.4 %	sulfonamides and trimethoprim
J01M	78,787	57,409	-27.1 %	quinolone antibacterials
J01A	48,368	42,672	-11.8 %	tetracyclines
J01G	1,054	856	-18.8 %	aminoglycoside antibacterials

Other changes appear considering the relative fractions of prescriptions in the same context, cf. Table 2.

Table 2: ATC 4 prescriptions 2019 and 2020.

ATC 4	frac. 2019	frac. 2020	diff.rel.	drug group
J01C	31.1 %	30.3 %	-2.8 %	beta-lactam antibacterials, penicillins
J01D	21.2 %	20.9 %	-1.4 %	other beta-lactam antibacterials
J01F	16.9 %	13.9 %	-17.5 %	macrolides, lincosamides and streptogramins
J01X	10.1 %	12.8 %	27.1 %	other antibacterials
J01E	7.4 %	8.1 %	9.2 %	sulfonamides and trimethoprim
J01M	8.1 %	7.9 %	-2.4 %	quinolone antibacterials
J01A	5.0 %	5.9 %	18.1 %	tetracyclines
J01G	0.1 %	0.1 %	8.7 %	aminoglycoside antibacterials

The largest absolute decrease occurs at "macrolides, lincosamides and streptogramins" (J01F), followed by "beta-lactam antibacterials, penicillins" (J01C) and "quinolone antibacterials" (J01M). The largest increase of the relative fractions occurs in the unspecific drug group "other antibacterials" (J01X), followed by "tetracyclines" (J01A) and the smallest group with absolute prescriptions numbers "aminoglycoside antibacterials" (J01G). The entropy e defined by $e = -\sum p_i ln(p_i)$ as a measure of distribution differences increases slightly from 0.772 to 0.785.

Prescription frequencies before the pandemic (2019) and at the beginning of the Corona pandemic (2020) are closely linked to the group of medical specialist prescribing. The largest decline in the number of prescriptions occurred among paediatricians (-41.0%), followed by ENT doctors (-33.6%) and general practitioners (-26.6%). There was a comparatively slight decline among gynaecologists (-3.2%), followed by dermatologists (-3.8%), surgeons (-3.5%) and urologists (-5.8%). Some ATC 4 drug groups are primarily used in antibiotics by certain specialist groups.

For the top 10 positions in terms of ATC 5 prescription frequency in 2019, the changes from 2019 to 2020 are shown in Table 3.

Table 3: ATC 5 prescriptions 2019 and 2020.

ATC 5	nr. 2019	nr. 2020	diff.rel.	drug group
J01CA	154,815	105,379	-31.9 %	beta-lactam antibacterials, penicillins
J01DC	152,422	101,789	-33.2 %	other beta-lactam antibacterials
J01FA	139,762	79,163	-43.4 %	macrolides, lincosamides and streptogramins
J01CR	87,871	75,945	-13,6 %	other antibacterials
J01MA	78,787	57,409	-27.1 %	sulfonamides and trimethoprim
J01XX	77,724	73,215	-5.8 %	quinolone antibacterials
J01EE	58,823	44,085	-25.1 %	tetracyclines
J01CE	57,101	36,017	-36.9 %	aminoglycoside antibacterials
J01AA	48,368	42,672	-11.8 %	tetracyclines
J01DD	45,120	45456	0,7 %	aminoglycoside antibacterials

The Drug group J01C (beta-lactam antibacterials, penicillins) splits in subgroups: J01CA (beta-lactam antibacterials, penicillins, -31.9%) and J01CE (beta-lactam antibacterials, penicillins, -36.9%) whith a marked decrease and J01CR (other antibacterials, -13.6%) slowly decreasing. The drug group J01D (other beta-lactam antibacterials, -26.4%) with decrease has the subgroup J01DD (aminoglycoside antibacterials, +0.7%) with increased in drug prescription numbers.

Next, we look at the ATC 7 drug level, cf. Table 4.

Table 4: ATC 7 prescriptions 2019 and 2020.

ATC 7	nr. 2019	nr. 2020	diff.rel.	drug group
J01CA04	147,205	91,798	-37,6 %	amoxicillin
J01DC02	112,231	77,543	-30,9 %	cefuroxime
J01FA10	79,345	46,094	-41,9 %	azithromycin
J01XX01	73,950	69,450	-6,1 %	fosfomycin
J01EE01	58,823	44,085	-25,1 %	sulfamethoxazole and trimethoprim
J01CR02	58,006	49,080	-15,4 %	amoxicillin and beta-lactase inhibitors
J01MA02	54,980	40,859	-25,7 %	ciprofloxacin
J01CE02	52,548	33,498	-36,3 %	phenoxymethylpenicillin
J01DD13	43,531	44,146	1,4 %	cefpodoxime
J01AA02	41,143	36,112	-12,2 %	doxycycline

Using the ATC 7, we have again a more differentiated picture on the level of active substances.

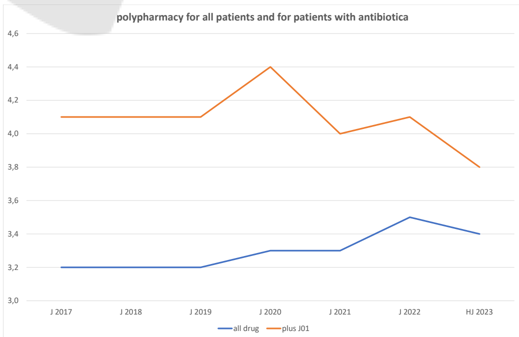

Figure 4: Time series for polypharmacy for all patients and for patients with antibiotic drugs.

We consider the mean number of prescribed active substances per patient at the ATC 7 level as a measure of polypharmacy with a quarter as time reference. This is considered for all patients as well as for those who get an antibiotic prescription. Assuming that the additional antibiotic prescription increases the level of polypharmacy by one, instead does not necessarily hold true, because patient groups may differ in their morbidity.

In the pre-Corona period, the difference was only slightly less than 1 at 0.9. At the beginning of the pandemic in 2020, the polypharmacy value rose significantly faster by 0.3 among antibiotic patients than by 0.1 among all patients. In the following year 2022, the polypharmacy value for all patients remains unchanged compared to 2021, while the value for antibiotic patients falls to 4.0, which is a lower value than in the pre-Corona period. This trend intensifies in the first half of 2023: There is an increase in all patients compared to 2021 and a reduction in antibiotic patients, thus the difference is only 0.4.

Antimicrobial resistance (AMR) is a threat to global health and development and it contributes to millions of deaths worldwide each year, so the WHO aims to improve the surveillance of antimicrobial resistance through a global action plan on AMR in order to reduce inappropriate antibiotic consumption. The WHO Categories Access, Watch, Reserve (AWaRe) provide concise, evidence-based guidance on the choice of antibiotic, dose and route of administration, cf. (World Health Organization, 2022b), (World Health Organization, 2022a). As access antibiotics show a narrow spectrum of activity, less side-effects, a lower potential for the selection of antimicrobial resistance and lower cost, they are recommended for the empiric treatment of most common infections and should be widely available. Watch antibiotics have a higher potential for the selection of antimicrobial resistance, therefore, their use should be restricted to sicker patients in hospital facility settings carefully monitored to avoid overuse. Reserve antibiotics are last-resort antibiotics that should only be used to treat severe infections caused by multidrug-resistant pathogens. The proportion of reserve antibiotics in our data is 0.17% for the entire period under consideration, with no significant deviations. The proportion of infections in the WHO "watch" category has fallen moderately since the beginning of our analyses until quarter 2 of 2021, cf. Figure 5. This will be related to extensive consultations with doctors on this topic in the Germen region of Schleswig-Holstein. Surprisingly, this trend remains almost the same at the beginning of the pandemic. Only in the third quarter of 2021, there is a significant change, namely towards an even greater drop in the WHO watch category fraction with a further moderate drop until the second quarter of 2022. After a moderate increase in the fourth quarter of 2022 and the first quarter of 2023, the proportion falls moderately again in the second quarter of 2023. In the middle part of the pandemic and also when it expires, the proportion of prescriptions in the WHO watch category showns a positive trend already significantly reduced before the pandemic. The extent to which this is caused by prescription behavior or by changing disease states should be investigated by further research.

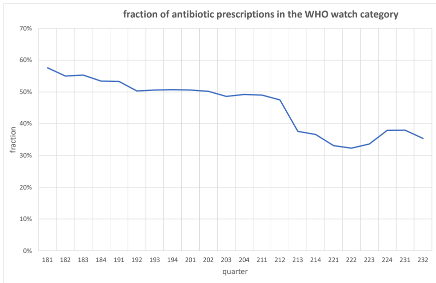

Figure 5: Prescription switch between drug groups within an antibiotic therapy 2021 with clusters.

Next, we consider therapeutic replacements of prescribed drug groups at different ATC-levels in 2018 before the pandemic and in 2021 during the pandemic. For each drug group, we determine the $n = 2$ other drug groups that it is most frequently replaced with, using at least 100 prescription changes as a threshold to reduce graphical complexity. We consider a graph visualisation with community clusters performed with Mathematica by Wolfram Research. The clusters are determined by minimizing the transitions between the clusters compared to the transitions within the clusters; about graph theory methods, see (Brooks, 1991), (Buser, 1978), (Chakrabarti and Faloutsos, 2006), (Chung, 1997) and (Alon, 1998).

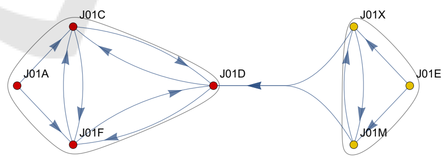

Figure 6: Prescription switch between drug groups within an antibiotic therapy 2018 with clusters.

The community cluster changed between 2018 (cf. Figure 6) and 2021 (cf. Figure 7) in J01M (quinolone antibacterials) forming an own minimal cluster in 2021 and J01D (other beta-lactam antibacterials) moving to the other primary cluster in 2018.

At ATC 5 level, there are major differences in the community clusters, 2018 (cf. Figure 8) showing three clusters and 2021 (cf. Figure 9) two cluster and one more vertex. The drug group J01CA (penicillins with extended spectrum) has one incoming edge in 2018 and five incoming edges in 2021, this drug group

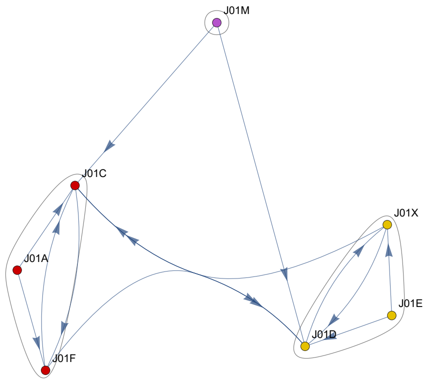

Figure 7: Prescription switch between drug groups within an antibiotic therapy 2021 with clusters.

Table 5: ATC 4 drug groups in transition graphs.

ATC 4	drug group
J01A	tetracyclines
J01C	beta-lactam antibacterials, penicillins
J01D	other beta-lactam antibacterials
J01E	sulfonamides and trimethoprim
J01F	macrolides, lincosamides and streptogramins
J01M	quinolone antibacterials
J01X	other antibacterials

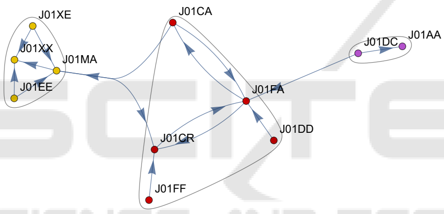

Figure 8: Prescription switch between drug groups within an antibiotic therapy 2018 with clusters.

was changed to another more frequently than another was changed to this group. Due to the extended spectrum of action of J01CA, the replacement may be motivated by theapeutic safety reasons, cf. (Holstiege et al., 2022), (Langford et al., 2021), (Kern et al., 2006) and (Filippini et al., 2006). Another possibility could be a change due to delivery difficulties.

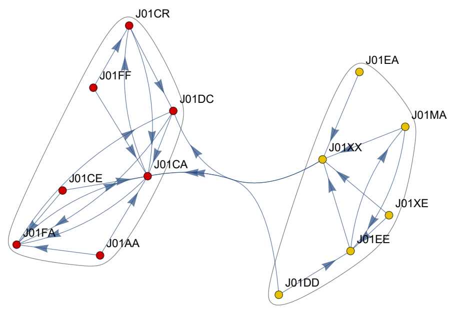

Figure 9: Prescription switch between drug groups within an antibiotic therapy 2021 with clusters.

Table 6: ATC 5 drug groups in transition graphs.

ATC 5	drug group
J01AA	tetracyclines
J01CA	penicillins with extended spectrum
J01CE	beta-lactamase sensitive penicillins
J01CR	combinations of penicillins, incl. beta-lactamase inhibitors
J01DC	second-generation cephalosporins
J01DD	third-generation cephalosporins
J01EA	trimethoprim and derivatives
J01EE	combinations of sulfonamides and trimethoprim, incl. derivatives
J01FA	macrolides
J01FF	lincosamides
J01MA	fluoroquinolones
J01XE	nitrofuran derivatives
J01XX	other antibacterials

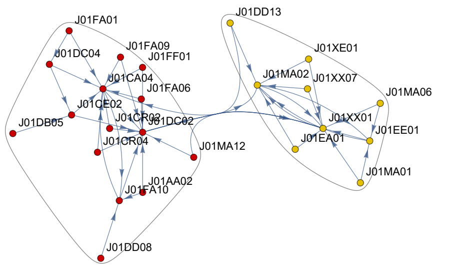

Figure 10: Prescription switch between drug groups within an antibiotic therapy 2018 with clusters.

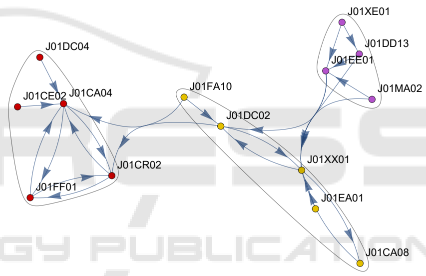

Figure 11: Prescription switch between drug groups within an antibiotic therapy 2021 with clusters.

Table 7: ATC 7 drug groups in transition graphs.

ATC 7	drug group
J01CA04	amoxicillin
J01CA08	pivmecillinam
J01CE02	phenoxymethylpenicillin
J01CR02	amoxicillin and beta-lactase inhibitors
J01DC02	cefuroxime
J01DC04	cefaclor
J01DD13	cefpodoxime
J01EA01	trimethoprim
J01EE01	sulfamethoxazole and trimethoprim
J01FA10	azithromycin
J01FF01	clindamycin
J01MA02	ciprofloxacin
J01XE01	nitrofurantoin
J01XX01	fosfomycin

In contrast to the ATC 4 and ATC 5 drug groups, the graph for the active ingredients according to ATC 7 is divided into two community clusters in 2018 and three in 2021. The active ingredients J01FF01 (clindamycin), J01CR02 (amoxicillin and beta-lactase inhibitors) and J01CA04 (amoxicillin) appear in pairwise and in both directions as the main versions of a therapy change.

4 DISCUSSION

The number of prescriptions for antibiotics in our data has risen back to the level of 2017 in 2022 after a sharp drop, particularly in 2020 being the first year of the pandemic. The WHO declared the outbreak of the novel coronavirus to be a public health emergency of international concern on January 30th 2020. The German parliament passed a first legal act on medical drugs on March 25th 2020 easing the formerly very restrictive regulations upon drug disposal, enabling the dispensing pharmacists to change the medically prescribed disposal variant and to exchange substitutional substances on their own judgement. Delivery bottlenecks for industrial produced antipyretic cough syrups for children were avoided by allowing pharmacists to supply individual preparations instead and by suspension of reimbursement limits for children preparations of drugs.

Since Germany rather met to a small part issues for antibiotic drugs during the pandemic, the prescription decrease observed may rather reflect a changed health situation. Staying at home during the lockdown in 2020 reduced the number of GP consultations in Germany (Kolbe, 2021) and telemedicine appointments took a full flight, replacing face-to-face contacts (Mangiapane et al., 2022), (Patel et al., 2021) and (Tarazi et al., 2021). Prior to the pandemic, respiratory tract infections and the need for a sick leave certificate were among the main reasons to consult a GP. The lockdown as well as the mitigation strategies such as mask wearing decreased the risk for coronavirus infection, but lowered the rate of influenza and all other respiratory tract infections as well (Lepak et al., 2021), (Olsen et al., 2020), (Nawrocki et al., 2021). To prevent the spread of coronavirus during the pandemic, legal restrictions have been relaxed to allow doctors to issue sick notes upon request by telephone. Employees presenting with respiratory tract infections, with fever or feeling unwell were encouraged to stay in remote work depending on their own judgement. In Belgium, respiratory tract infections were found to be the main diagnosis for overprescribing of antibiotics by GPs (Colliers et al., 2019), (Smits et al., 2019). As shown in Table 8, most of the drugs prescribed in our study can contribute to antibiotic drug resistance (Ventola, 2015). Antibiotic drug resistance was described for the first time for penicilline in 1940.

Affecting more and more substances, antibiotic resistance represents a serious health threat worldwide now (European Centre for Disease Prevention and Control, 2020). The phenomenon of poly drug resistance emerging in 2009 worsens this critical public health situation (Ventola, 2015). As there is only limited financial interest in the market (Astrup et al., 2017), we lack the development of new antibiotic drugs and keep prescribing substances that entered the market several decades ago. Previous exposure to antibiotics is a key driver for antibiotics resistance (Chatterjee et al., 2018). Inappropriate prescribing of antibiotic drugs fuels antibiotic resistance, so it is crucial to limit the treatment with watch (and reserve) antibiotics to intensive care patients as a last resort. Thanks to antibiotic stewardship programs, Germany got off to a flying start ranking fifth among 30 European countries with one of the lowest amounts of outpatient prescription of antibiotics at the begin of the pandemic, (European Centre for Disease Prevention and Control, 2020).

Table 8: Cross linking our data with the list by Ventola 2015 for reports upon antibiotic resistance in the U. S..

ATC Codes	Our data	ATC/ introduction/ drug	Resistance reports
J01C	**Penicilline and beta-lactam AB**		
J01CA04	amoxicilline	J01C penicilline	1940 Staphylococcus
J01CA08	piymecillinam		1965 Pneumococcus
J01CR02	amoxicilline and beta-lactamase inh.		
J01CE02	phenoxymethylpenicillin		
J01D	**Other beta-lactam AB**		
J01DC02	cefuroxime (3rd gen)	J01DD02 1985 ceftazidin 3rd gen	1987 Enterobacter
J01DC04	cefaclor (2nd gen)	J01DD04 1982 ceftriaxon 3rd gen	2009 Neisseria gon.
J01DD13	cefpodoxim (2nd gen)	J01DI02 2010 ceftaroline 5th gen	2011 Staphylococcus
J01F	**Macrolide, lincosamide, streptogramine**		
J01FA10	azithromycine	J01CF03 1960 methicilline	1962 Staphylococcus
J01FF01	clindamycine	J01FA01 1953 erythromycin	1968 Streptococcus
J01E	**Sulfonamide and trimethoprim**e		
J01EA01	trimethriprime	J01XA01 1972 Vancomycin	1988 Enterococcus
J01EE01	sulfamethoxazole trimethroprime		2002 Staphylococcus
J01EE01	sulfamethoxazole trimethroprime		2004 Acinetobacter
J01EE01	sulfamethoxazole trimethroprime		2005 Pseudonomas
J01X	**Other AB**		
J01CE01	nitrofurantoine	J01XX08 2000 linezolide	2001 Staphylococcus
J01XX01	fosfomycine		
J01M	**Quinolone AB**		
J01MA02	ciprofloxacine	J01MA12 1996 Levofloxacin	1996 pneumococcus
J01AA	tetracycline		
J01AA02	doxycycline	J01AA 1950 tetracycline	1959 Shigella
J01G	**Aminogycoside AB**		
J01GB03		J01GB03 1967 gentamicine	1979 Entereococcus

Nevertheless, the prescription pattern for all antibiotics dropped again considerably with the onset of the pandemic. Other countries, show an increased prescription for the macrolide antibiotic azithromycin

(J01FA10) at the beginning of the pandemic (Colliers et al., 2021). It remains unclear if it was applied to treat suspected opportunistic co-infections or "just in case". In the US, the empiric treatment with antimicrobial drugs was explicitly repurposed, resulting in an increase in the general prescription of tetracycline (J01AA) and an increased prescription pattern in long-term care settings regarding azithromycin (J01FA10), (Kolbe, 2021). Large-scale empirical prescriptions carry the risk of new resistance developments, as previously described for both of these antibiotics, refer to Table 8. Our data show a decrease of prescription for all antibiotic drugs in Germany. In Belgium, after the short initial increase of azithromycin had passed, the prescription of antibiotics decreased considerably, too. Instead, there was no decrease for one of the first-choice antibiotic drugs for urinary tract infections, nitrofurantoin (Colliers et al., 2021). In our data, the prescription of nitrofurantoin (J01CE01) showed no different prescription pattern, decreasing in the same way as all other antibiotic drugs did.

5 CONCLUSION

After a sharp drop in 2020, the first year of the pandemic, the number of prescriptions for antibiotics in 2022 equals the prescription level in 2017. This overall decline in prescription rates for all and especially critical antibiotics observed in our data and in other regional studies as well suggests an effective implementation of the antibiotic stewardship program in Germany (Scholle et al., 2022).

Indeed, our data indicates an increase in the mean age of all patients receiving pharmacotherapy, including those receiving antibiotic therapy. This suggests potential health issues for middle-aged and older patients that go beyond demographic changes. The consequences of the COVID-19 pandemic continue to pose a challenge to the healthcare system and will remain a focus of research.

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