BELMAP

ONE HEALTH REPORT ON ANTIBIOTIC USE AND RESISTANCE

2011-2020

BELGIAN ACTION PLAN
AMR
One Health

EDITORIAL

Since 1999, the Belgian Antibiotic Policy Coordination Committee (BAPCOC) aims to improve antimicrobial stewardship in both human and veterinary medicine. Improving antimicrobial therapy will reduce the spread of in particular untreatable bacterial and fungal infections due to acquired resistance. On the basis of guidelines issued in 2019, and in agreement with the Strategic Cells of the Federal Ministers and with the federated Entities, the FPS Health, Food Chain Safety and Environment has coordinated the development of a National Action Plan (NAP) responding to the “One World, One Health” approach in order to fight against antimicrobial resistance (AMR).This plan was finally approved by all competent authorities in November 2021. In all discussions leading to the NAP-AMR, it was acknowledged that surveillance is a key tool to improve empirical guidelines, to guide infection control policies and intervention strategies, and to steer research agendas.

Well-established national monitoring programs exist for both the consumption of antimicrobial agents (AMC) and the occurrence of AMR in bacteria isolated from humans, food-producing animals and the food chain, as well as for antimicrobial residues in the environment. The different programs are organized with different aims and primary purposes. Given the scattered landscape and the vast majority of numerous databases, stakeholders and reports (Sanitel-Med, Sciensano, RIZIV/INAMI, EARS-BE, BeH-SAC, FASFC, etc.), it is challenging to retain a clear overview of the evolution of AMR and AMC across sectors in Belgium. One of the actions defined in the NAP-AMR is therefore the creation of a ‘One Health’ report on AMC and AMR in Belgium, much like leading countries in the field such as Denmark, France and The Netherlands.

The BELMAP report aims to summarize results and trends of existing monitoring programs, to identify blind spots and to make recommendations to improve future monitoring. To provide a clear overview of the situation in Belgium, a cross-sectorial editorial board was installed which agreed on **key indicators** for monitoring antibiotic use and resistance. These are inspired on indicators proposed by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) in 2017, but modified in BELMAP to reflect the current situation and the One Health aspect of AMR. We specifically expanded our efforts to resistance to antifungals, and included colistin resistance as a One Health indicator. These indicators will be yearly evaluated, based on the evolution of the AMR epidemiology. Importantly, **BELMAP 2021 does not replace the detailed sectorial reporting**. We refer the interested reader to separate annual veterinary and human monitoring reports, of which the references can be found in the footnotes.

This first overarching report is published during the declining phase of the SARS-CoV-2 pandemic. This period has had a major impact on the prevalence of communicable diseases in society, as well in the areas of antibiotic use and resistance. The most dramatic change was the decrease in antibiotic prescriptions in the human community sector, due to behavioral change and reduced social and health care visits. We are hopeful that the lessons learned during the pandemic, and the ambitious actions of the NAP-AMR, can have a lasting impact on consumption of antibiotics and antimicrobial resistance in humans, animals and the environment.

We wish you a pleasant and informative read.

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1 EXECUTIVE SUMMARY

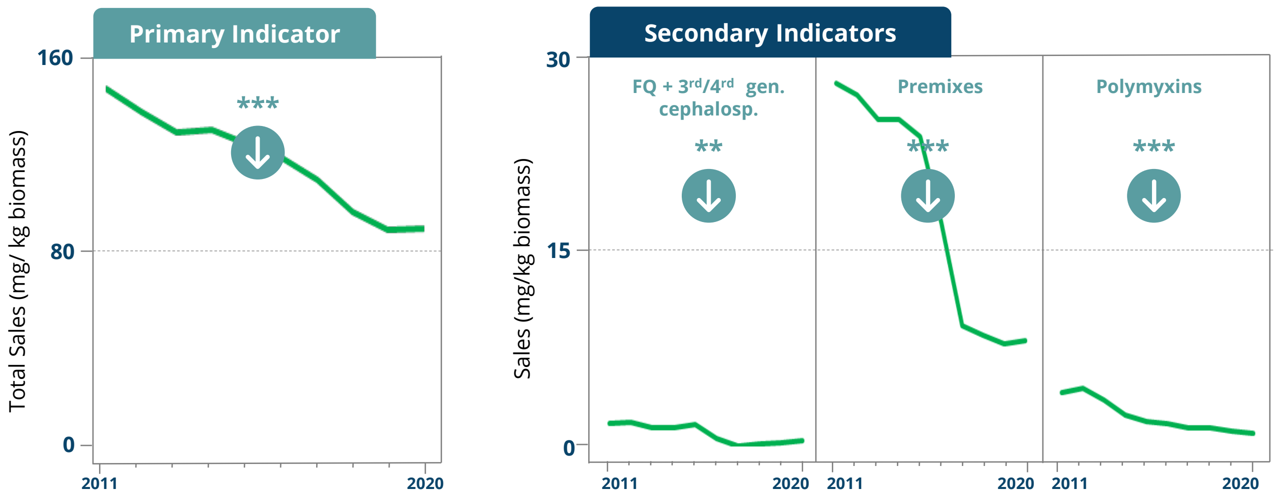
BELMAP makes use of key outcome indicators to summarize trends in antimicrobial consumption (AMC) and antimicrobial resistance (AMR) in humans and food-producing animals in Belgium. The selected indicators, slightly modified from those recommended by ECDC, EFSA and EMA in 2017[1], are divided into primary and secondary indicators.

Primary indicators broadly reflect the situation concerning AMC and AMR. They do not cover all aspects of AMC and AMR epidemiology and remain arbitrary, but can be used to provide a **general assessment of the overall situation**. Secondary indicators are designed to provide information on more specific issues that are also considered of importance for public health, but have a more restricted scope, or to encompass areas that are not fully covered by the primary indicator. With the exception of the proposed human AMR indicators, the indicators are in general not suitable by themselves to monitor the effects of targeted interventions in a specific sector, such as in a single animal species or animal production sector[1]. The level of statistical significance of up-and downward trends are indicated with asterisks.

ANTIMICROBIAL CONSUMPTION

Veterinary sector

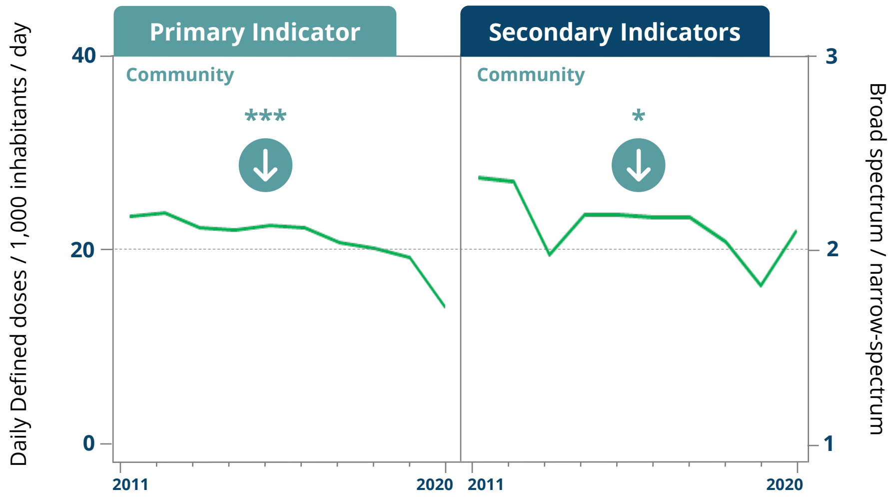
The consumption of antimicrobials in the veterinary sector, measured in total sales (mg/kg biomass), has decreased strongly since 2011. Data shows a cumulative reduction of 40.2% in 2020, which included a slight increase in the year. The decline is even more evident in the secondary indicators, as critically important antibiotics (fluoroquinolones and cephalosporins of 3rd and 4th generation) had a cumulative reduction of 70.1% in 2020 compared to 2011. A similar reduction (71.3%) was achieved for polymyxins, while antibacterial premixes[2] had a significant cumulative reduction of 70.4% in the same period.



In Belgium, the use of antibiotics per sector and animal category level is monitored since 2018, and expressed as BD100 or the percentage of time an animal is treated with antibiotics. In the measured period, a reduction of the median BD100 is only apparent in veal calves. However, this remains the sector with the highest antibiotic use, closely followed by the weaners in pigs.

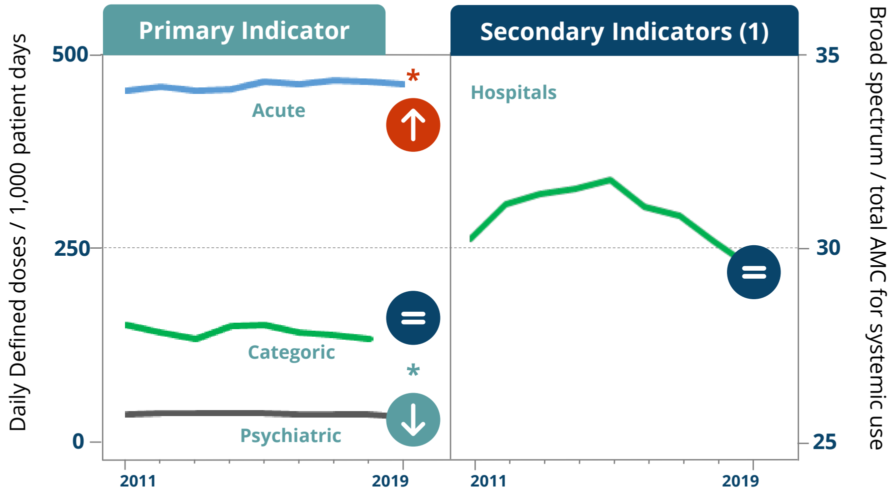
Human sector

The last decade has seen a considerable reduction in antimicrobial use in the **community**. From 2010 to 2019, we noted a statistical significant reduction of 14% in reimbursed antibiotics. During the Covid-19 pandemic, a strong additional reduction was observed, which might had to do with the changed pattern of care during the pandemic.

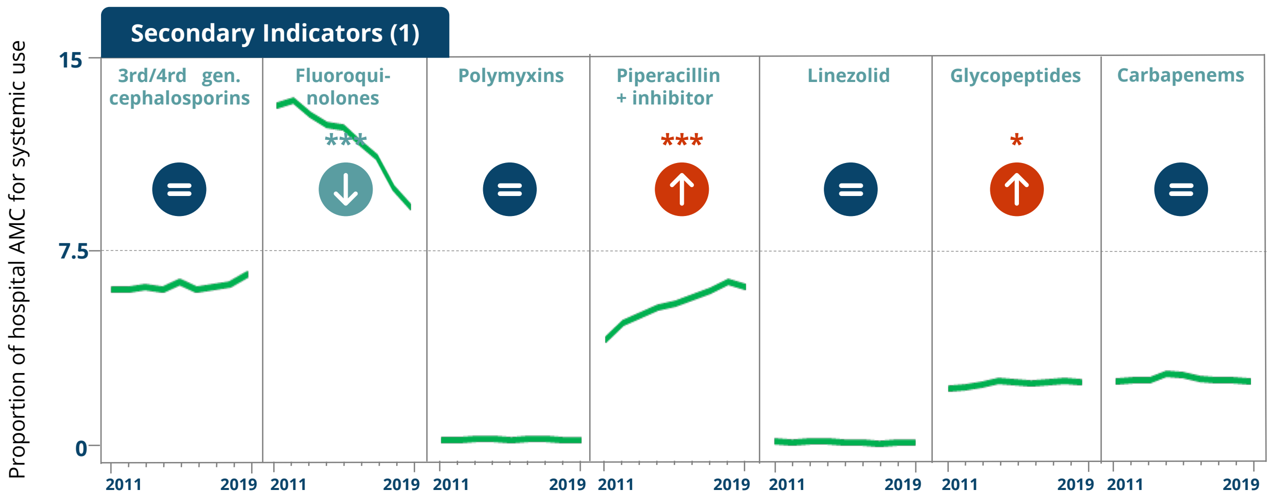


The ratio of amoxicillin to amoxicillin/clavulanic acid improved only slightly in the last decade (from 46/54 in 2010 to 51/49 in 2019), and is still far from the BAPCOC target of 80/20. Likewise, the targeted reduction in proportional use of fluoroquinolones (5% in 2018) was not reached: 6.7% in 2019, taking non-reimbursed consumption into account. On the positive side, the overall ratio of broad[3]-to-narrow spectrum antibiotics declined significantly.

In the **Belgian acute care hospitals** (data 2011-2019), around 450 Defined Daily Doses (DDDs) per 1000 patient days are recorded, and this use slightly increased (3%) over the last decade. Large differences exist between acute, categorical[4] and psychiatric hospitals, also when compared per type of hospital (primary, secondary, tertiary). The proportion of broad-spectrum use in Belgian hospitals (29.5% in 2019) did only slightly (but not significantly) improve over time. Also for this parameter, a high variation between hospitals has been reported in BeH-SAC.



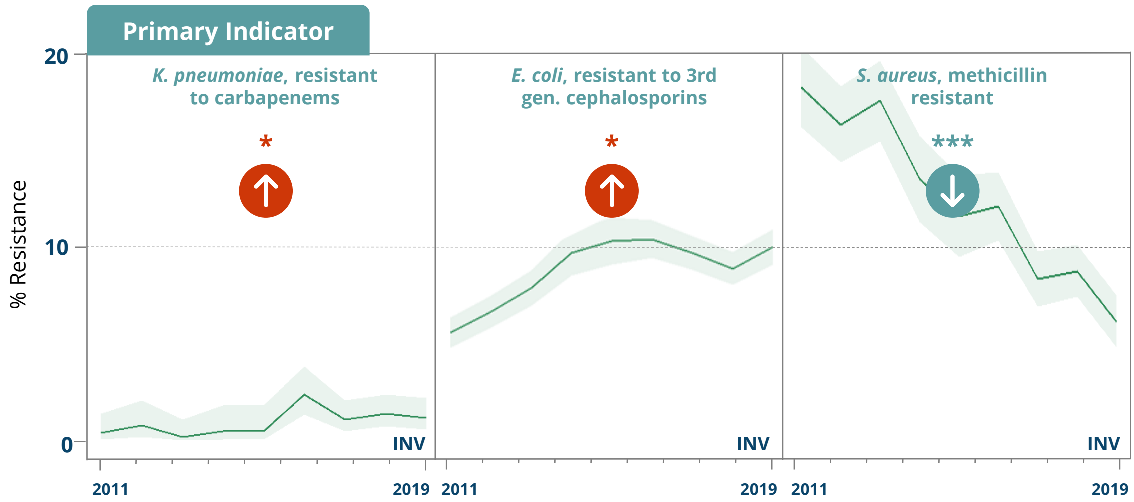
Looking at the proportions of the total hospital AMC which are broad-spectrum antibiotics, a very significant decrease is observed in the use of fluoroquinolones (-27% between 2011 and 2019). In contrast, the proportion of piperacillin in combination with tazobactam (+48%) and glycopeptides (+12%) significantly increased over time, although the increase in glycopeptides use was limited to 2011-2013.



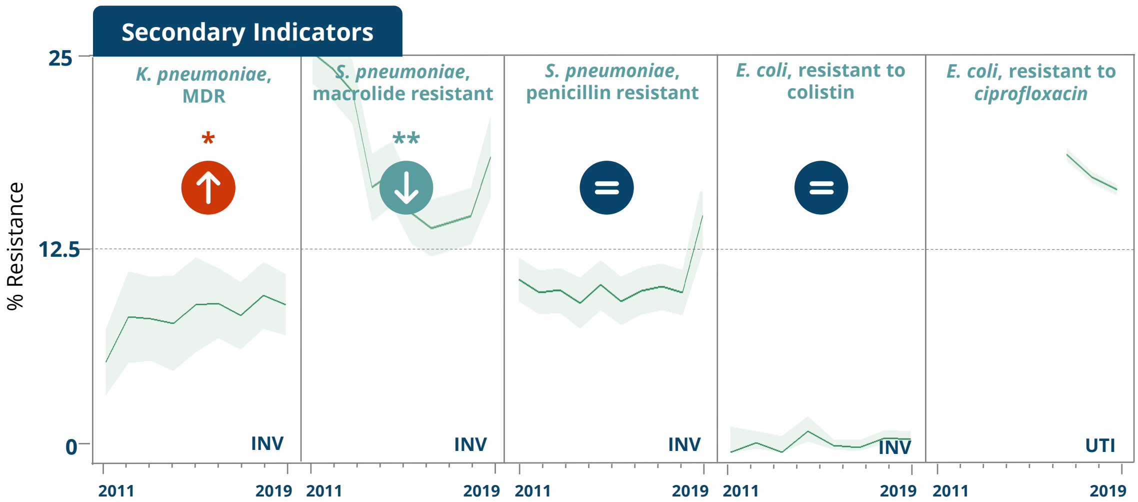
ANTIMICROBIAL RESISTANCE

Among human pathogens

BELMAP proposes slight modifications to the key indicators for AMR in human pathogens, proposed in 2017 by EMA/ECDC[1]. The prevalence of carbapenem-resistant *K. pneumoniae* was prioritized as primary indicator, and ciprofloxacin resistance in *Salmonella* and *Campylobacter spp.* were removed from the secondary indicator list, reflecting their clinical importance.



INV: Bacterial isolates from clinical invasive samples (blood and cerebrospinal fluid)



UTI: Isolated from urinary tract infections. No trend analysis given limited data availability

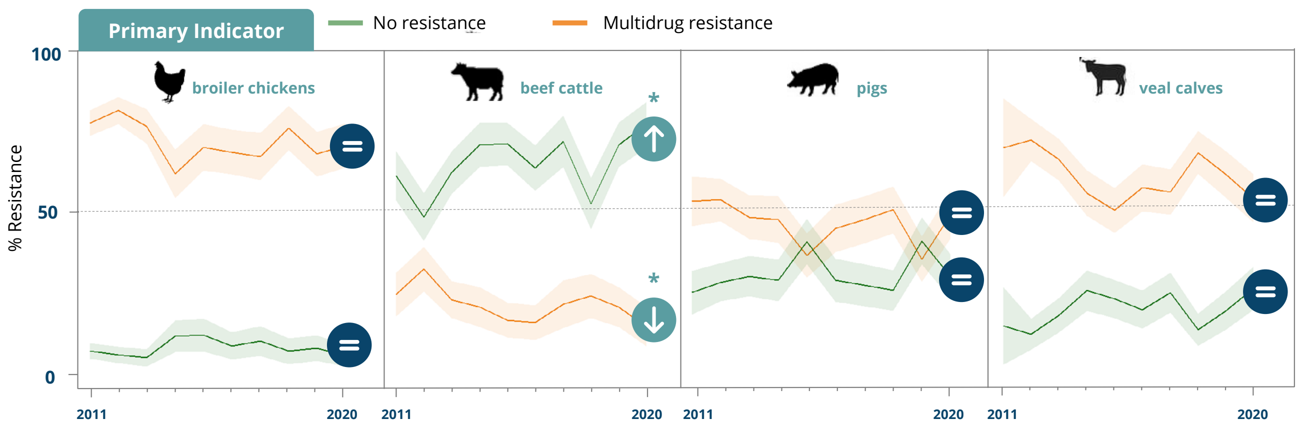
In the last decade, the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates declined strongly and continuously in Belgium. This contrast the growing proportion of invasive *E. coli* isolates resistant to 3rd generation cephalosporin, although a stabilization around 10% is observed after 2014. The prevalence of carbapenem-resistant *K. pneumoniae* over this time period increased significantly and reached 1.2% in 2019. The proportion of multi-drug resistant (MDR) *K. pneumoniae* strains, resistant to 3rd generation cephalosporins, aminoglycosides and fluoroquinolones, increased slightly (2011-2014) and then stabilized around 10%, which remains lower compared to the (declining) European mean. Colistin resistance in pathogenic *E. coli*, added to the key indicators to account for the use of polymyxins in both humans and animals, remains below 1%.

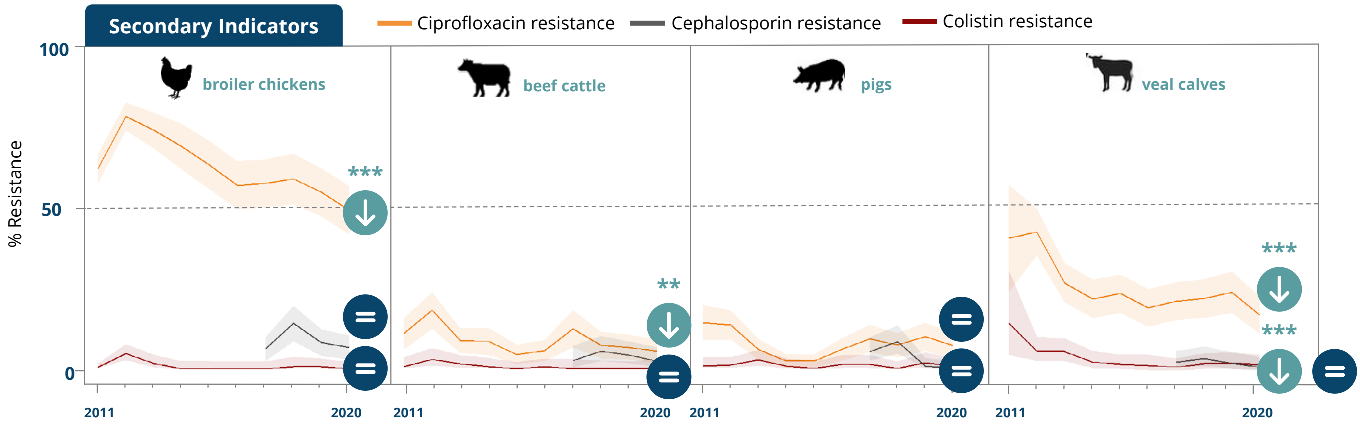
In 2020, an increase in penicillin resistance was observed among invasive *S. pneumoniae* strains, contrasting a stable penicillin resistance rates of 10% (2011-2019). This might have resulted from a switch in interpretation of susceptibility testing results at the National Reference Center (NRC) in 2019, and a substantial reduction in the number of collected samples in 2020. For macrolides, a similar increase was seen during the Covid-19 crisis, contrasting an initial decline and a stable resistance rate of about 15% for the period 2015-2019.

Among indicators isolated from healthy food-producing animals

Due to lack of publicly available data on AMR in animal pathogens, BELMAP uses AMR data on commensal bacteria from healthy animals as a general indicator for resistance among food-producing animals. They can acquire and preserve resistance genes from other organisms in the environment and in animal populations. Therefore, their resistance levels reflect the magnitude of the pressure exerted by antibiotics in the population.

Large differences exist between the animal groups. The highest proportion of fully sensitive *E. coli* strains are isolated from beef cattle, with a significant increase in susceptible strains and a record level of 78% pan-susceptible strains in 2020. Likewise, the proportion of multidrug resistant (MDR) *E. coli* declined significantly between 2011 and 2020 in this animal population. In the three other monitored food producing animal populations (broiler chickens, pigs and veal calves), no significant changes in the proportion of fully susceptible and MDR *E. coli* strains are observed (2011-2020). The levels of MDR *E. coli* are highest in poultry.





In poultry, beef cattle and veal calves, we observe significant decreases in ciprofloxacin resistance considering the entire 2011-2020 period, reaching its lowest levels in 2020. Likewise, the occurrence of colistin resistance in veal calves declined significantly. For all other species, the prevalence of the ciprofloxacin, colistin and cephalosporin resistance remained stable and very low, i.e. below 10% over the years.

Questions and remarks on BELMAP 2021 :

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1 RÉSUMÉ

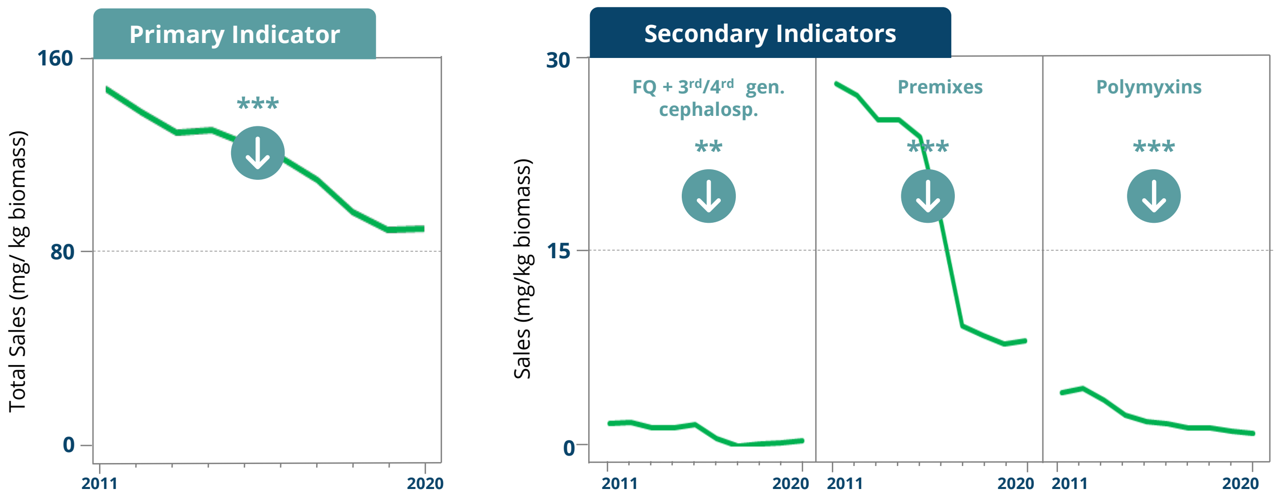
Le BELMAP utilise des indicateurs clés pour résumer les tendances de la consommation d'antimicrobiens (AMC) et de la résistance aux antimicrobiens (AMR) chez l'homme et les animaux producteurs d'aliments en Belgique. Les indicateurs sélectionnés, légèrement modifiés par rapport à ceux recommandés par l'ECDC, l'EFSA et l'EMA en 2017[1], sont répartis en indicateurs primaires et secondaires.

Les indicateurs primaires reflètent globalement la situation concernant l'AMC et l'AMR. Ils ne couvrent pas tous les aspects épidémiologiques de l'AMC et l'AMR et demeurent arbitraires, mais peuvent être utilisés pour fournir une **évaluation générale de la situation globale**. Les indicateurs secondaires sont conçus pour fournir des informations sur des questions plus spécifiques qui sont également considérées comme importantes pour la santé publique, mais dont la portée est plus restreinte, ou pour englober des domaines qui ne sont pas entièrement couverts par l'indicateur primaire. À l'exception des indicateurs proposés pour l'AMR chez l'homme, les indicateurs ne sont généralement pas destinés en tant que tels à surveiller les effets d'interventions ciblées dans un secteur spécifique, par exemple dans une seule espèce animale ou un seul secteur de production animale[1].

CONSOMMATION D'ANTIMICROBIENS

Secteur vétérinaire

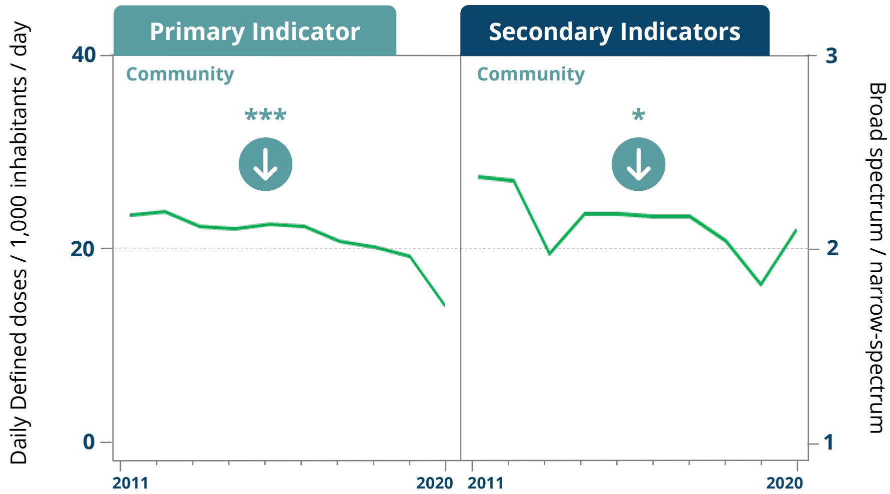
La consommation d'antimicrobiens dans le secteur vétérinaire, mesurée en ventes totales (mg/kg de biomasse), a **fortement diminué** depuis 2011. Les données montrent une réduction cumulée de 40,2 % en 2020, qui comprend une légère augmentation au cours des dernières périodes considérées. La baisse est encore plus évidente dans les indicateurs secondaires, car les antibiotiques d'importance critique (fluoroquinolones et céphalosporines de 3ème et 4ème génération) ont connu une réduction cumulée de 70,1% en 2020 par rapport à 2011. Une réduction similaire (71,3 %) a été obtenue pour les polymyxines, tandis que les prémélanges[5] antibactériens ont connu une réduction cumulative significative de 70,4 % au cours de la même période.



En Belgique, l'utilisation d'antibiotiques par secteur et par catégorie d'animaux est enregistrée depuis 2018, et exprimée en BD100 correspondant au pourcentage de temps pendant lequel un animal est traité avec des antibiotiques. Au cours de la période considérée, une réduction significative du BD100 médian n'a été obtenue que chez les veaux de boucherie. Toutefois, ce secteur reste celui qui utilise le plus d'antibiotiques, suivi de près par le secteur des porcelets sevrés.

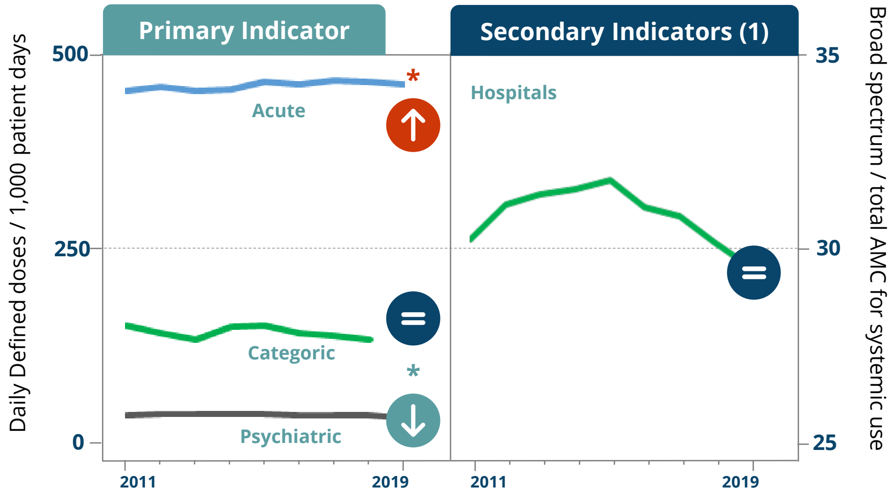
Secteur humain

La décennie précédente a vu une réduction considérable de l'utilisation des antimicrobiens dans la **pratique ambulatoire**. De 2010 à 2019, on a constaté une réduction statistiquement significative de 14% de l'utilisation des antibiotiques remboursés. Pendant la pandémie de Covid-19, une forte réduction additionnelle a été observée, ce qui pourrait être lié au changement du mode de soins pendant la pandémie.

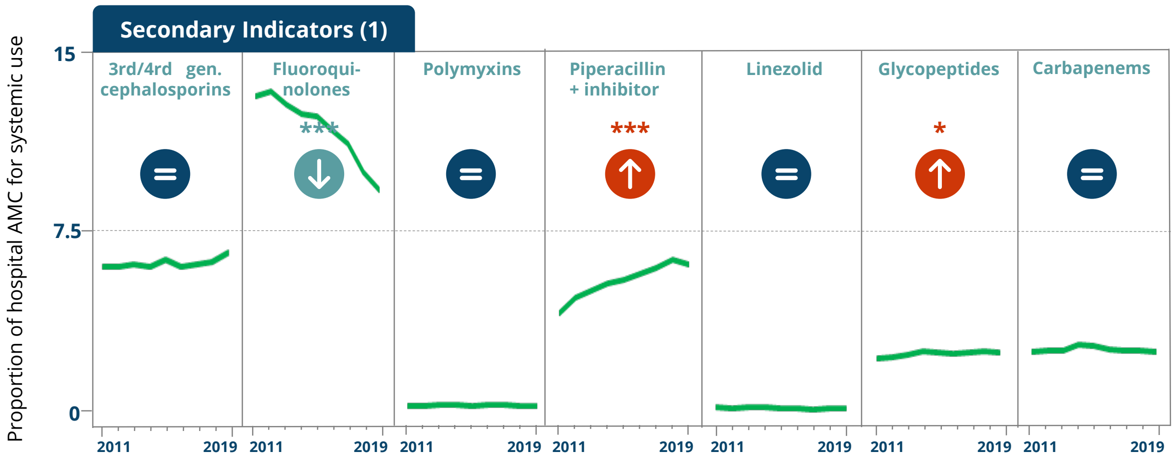


Le rapport entre l'amoxicilline et l'amoxicilline/acide clavulanique ne s'est que légèrement amélioré au cours de la dernière décennie (de 46/54 en 2010 à 51/49 en 2019), et est encore loin de l'objectif de 80/20 fixé par le BAPCOC. De même, la réduction ciblée de l'utilisation proportionnelle des fluoroquinolones (5% en 2018) n'a pas été atteinte : 6,7% en 2019, en tenant compte de la consommation non remboursée. Du côté positif, le ratio global des antibiotiques à spectre large[6] par rapport aux antibiotiques à spectre étroit a sensiblement diminué.

Dans les **hôpitaux belges de soins aigus** (données 2011-2019), environ 450 doses journalières définies (Defined Daily Dose, DDD) sont enregistrées pour 1000 jours-patients, et cette utilisation a légèrement augmenté (3%) au cours de la dernière décennie. De grandes différences existent entre les hôpitaux de soins aigus, chroniques et psychiatriques. Elles s'observent également lorsqu'on les compare par type d'hôpital (primaire, secondaire, tertiaire). La proportion d'utilisation d'antibiotiques à spectre large dans les hôpitaux belges (29,5% en 2019) ne s'est que légèrement (mais pas significativement) améliorée au fil du temps. Pour ce paramètre également, une forte variation entre les hôpitaux a été rapportée dans le BeH-SAC.



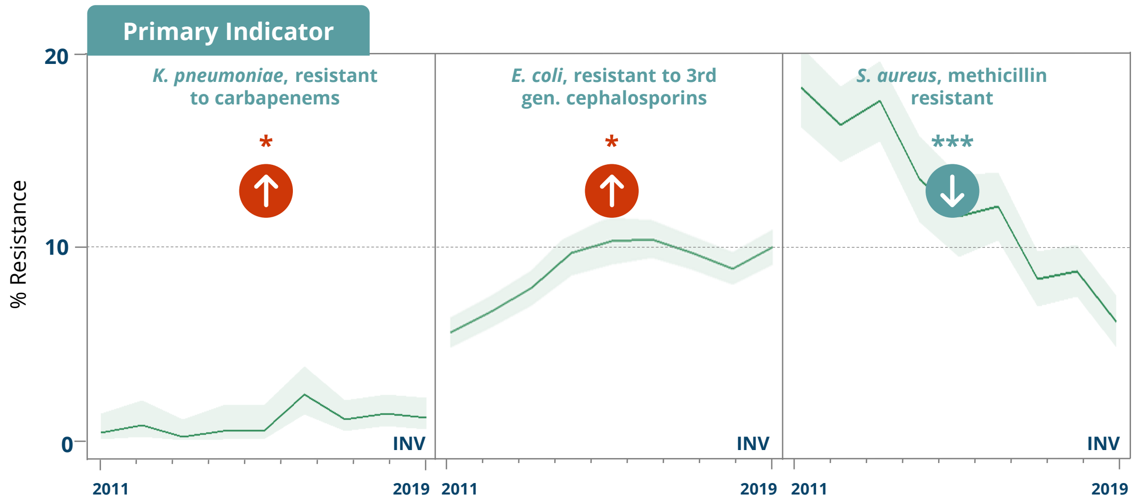
Pour les AMC relatives aux antibiotiques à large spectre dans le secteur hospitalier, une diminution très significative de l'utilisation des fluoroquinolones est observée (-27% entre 2011 et 2019). En revanche, la proportion de pipéracilline en association avec le tazobactam (+48%) et de glycopeptides (+12%) a significativement augmenté au fil du temps. L'augmentation de l'utilisation des glycopeptides s'est néanmoins limitée à la période 2011-2013.



RÉSISTANCE AUX ANTIMICROBIENS

Parmi les agents pathogènes humains

Le BELMAP propose de légères modifications des indicateurs clés de l'AMR proposés en 2017 par l'EMA/ECDC[1] pour les pathogènes humains. La prévalence de *K. pneumoniae* résistante aux carbapénèmes a été considérée comme un indicateur primaire et la résistance à la ciprofloxacine chez *Salmonella* et *Campylobacter spp*. a été retirée de la liste des indicateurs secondaires.



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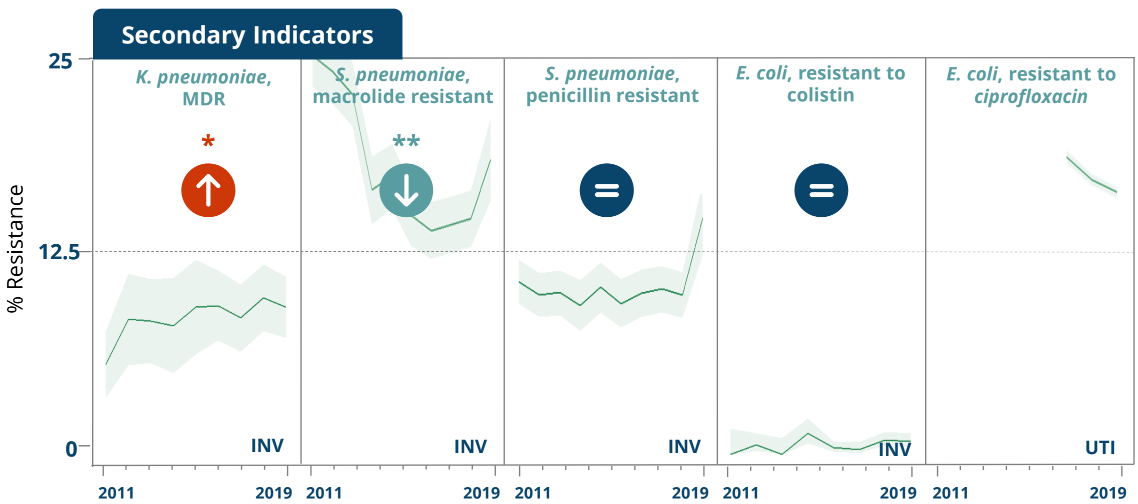


UTI: Isolated from urinary tract infections. No trend analysis given limited data availability

Au cours de la dernière décennie, la proportion d'isolats de *Staphylococcus aureus* résistants à la méthicilline (MRSA) a fortement et continuellement diminué en Belgique. Ceci contraste avec la proportion croissante d'isolats cliniques d'*E. coli* résistants aux céphalosporines de 3ème génération, bien qu'une stabilisation autour de 10% soit observée après 2014.

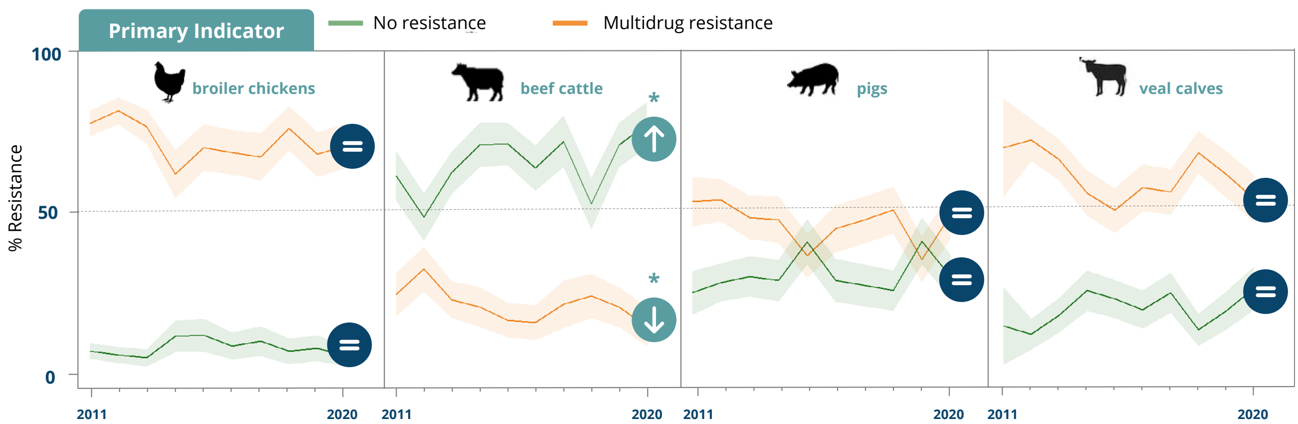
La prévalence de *K. pneumoniae* résistant aux carbapénèmes sur cette période a augmenté et a atteint 1,2% en 2019. La proportion de souches de *K. pneumoniae* multirésistantes (MDR), résistantes aux céphalosporines de 3e génération, aux aminoglycosides et aux fluoroquinolones, a légèrement augmenté (2011-2014) puis s'est stabilisée autour de 10 %, ce qui reste inférieur à la moyenne européenne (en baisse). La résistance à la colistine chez les *E. coli* pathogènes, ajoutée aux indicateurs clés pour tenir compte de l'utilisation des polymyxines chez l'homme et l'animal, reste inférieure à 1%.

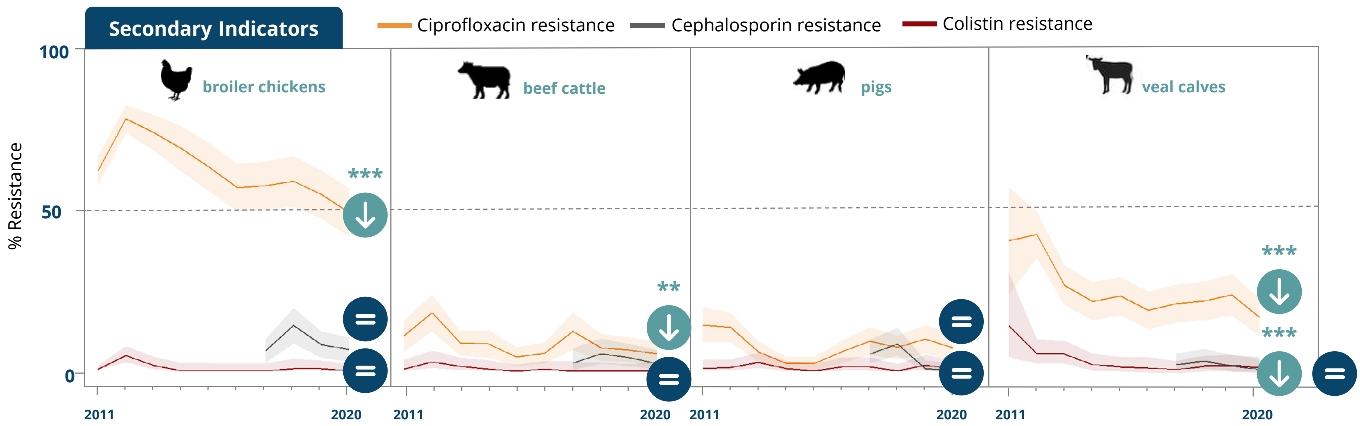
En 2020, une augmentation de la résistance à la pénicilline a été observée parmi les souches invasives de *S. pneumoniae*, contrastant avec une stabilité des taux de résistance à la pénicilline de 10% (2011-2019). Cela pourrait être dû à un changement d'interprétation des résultats des antibiogrammes au Centre national de référence (CNR) en 2019, et à une réduction substantielle du nombre d'échantillons collectés en 2020. Pour les macrolides, une augmentation similaire a été observée pendant la crise du Covid-19, contrastant avec une baisse initiale et un taux de résistance stable d'environ 15 % pour la période 2015-2019.

Parmi les animaux sains destinés à la production de denrées alimentaires

En raison du manque de données publiques sur l'AMR chez les pathogènes animaux, le BELMAP utilise les données sur l'AMR des bactéries commensales d'animaux sains comme indicateur général de la résistance chez les animaux destinés à l'alimentation. Elles peuvent acquérir et conserver des gènes de résistance provenant d'autres organismes dans l'environnement et dans les populations animales. Par conséquent, leurs niveaux de résistance reflètent l'ampleur de la pression exercée par les antibiotiques dans la population.

De grandes différences existent entre les groupes d'animaux. La plus grande proportion de souches d'*E. coli* totalement sensibles est isolée chez les bovins, avec une augmentation significative de souches pan-sensibles vers un niveau record de 78 % en 2020, et une réduction significative de souches multirésistants. Dans les trois autres populations animales productrices de denrées alimentaires surveillées (poulets de chair, bovins de boucherie, porcs et veaux de boucherie), on n'observe de changements significatifs dans la proportion de souches d'*E. coli* totalement sensibles (2011-2020). Les niveaux d' *E. coli* multirésistants sont les plus élevés chez les volailles.





Chez les volailles, les bovins et les veaux de boucherie, nous observons une diminution significative de la résistance à la ciprofloxacine sur l'ensemble de la période 2011-2020, atteignant ses niveaux les plus bas en 2020. De même, l'occurrence de la résistance à la colistine chez les veaux de boucherie a diminué de manière significative. Pour toutes les autres espèces, la prévalence de la résistance à la ciprofloxacine, à la colistine et aux céphalosporines est restée stable et très faible, c'est-à-dire inférieure à 10 % au fil des années.

Questions et remarques sur BELMAP 2021 :

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1 SAMENVATTING

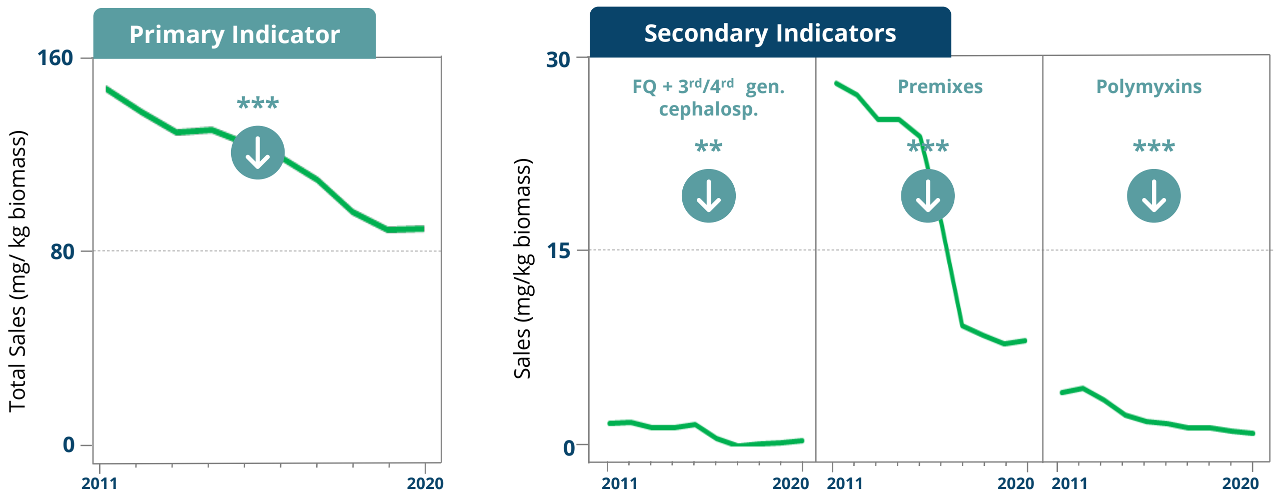
BELMAP maakt gebruik van indicatoren om nationale trends in het gebruik van, en resistentie tegen antimicrobiële middelen in mens en dier samen te vatten. Deze indicatoren werden op Europees niveau gedefinieerd door experts van ECDC, EFSA en EMA in 2017[1], en werden opgesplitst in primaire en secondaire indicatoren.

Primaire indicatoren reflecteren de **algemene situatie** wat betreft antibioticagebruik en -resistentie. Hoewel ze arbitrair zijn en uiteraard maar bepaalde aspecten van de epidemiologie belichten, laten ze wel toe een algemeen beeld te schetsen van de situatie. Secundaire indicatoren richten zich op topics die ook van belang zijn voor de volksgezondheid, maar specifieker zijn of niet worden weergegeven door de primaire indicator. Met uitzondering van de indicatoren voor resistentie bij humane stalen, zijn deze op zichtzelf onvoldoende om het effect te beoordelen van specifieke interventies in een specifieke sector[1].

ANTIMICROBIËLE CONSUMPTIE

Veterinaire sector

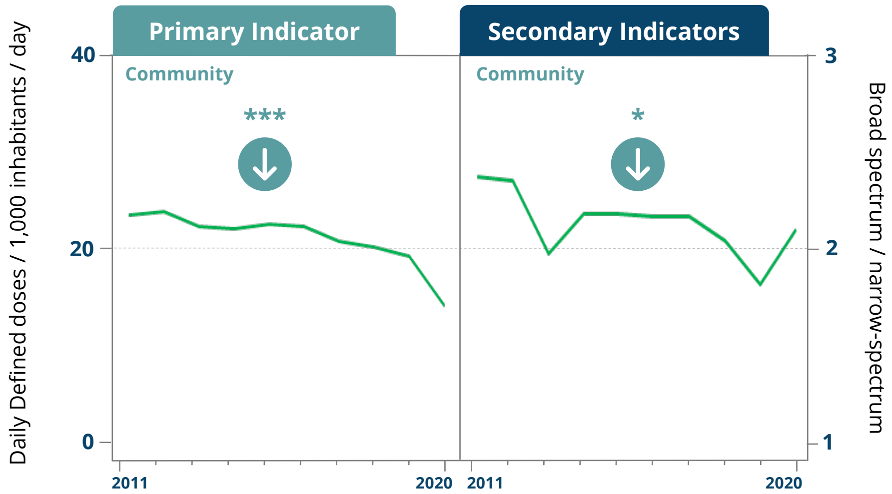
Het gebruik van antibacteriële middelen in de veterinaire sector, gemeten aan de hand van de totale verkoop (mg/kg biomassa), is **sterk afgenomen** sinds het begin van de metingen in 2011. De data toont een cumulatieve reductie van 40.2% over tien jaar. De afname is zelfs nog meer uitgesproken zichtbaar in de secundaire indicatoren, waar in het gebruik van kritische antibiotica (fluoroquinolones en cefalosporines van de 3de en 4de generatie) een cumulatieve reductie toont van 70.1% sinds 2011. In deze periode werd een gelijkaardige reductie bereikt voor de polymyxins (71.3%) en voor de antibacteriële premixen[7] (70.4%).



In België wordt vanaf 2018 het gebruik van antibiotica per sector en diercategorie opgevolgd, en uitgedrukt in BD100, het percentage van de tijd dat een dier wordt behandeld met antibiotica. In de drie jaar waarvoor al data beschikbaar is (2018-2020) werd er enkel een opvallende reductie van de BD100 geobserveerd bij de vleeskalveren. Dit blijft echter de sector met het hoogste gebruik van antibiotica, kort gevolgd door de spenen in varkens.

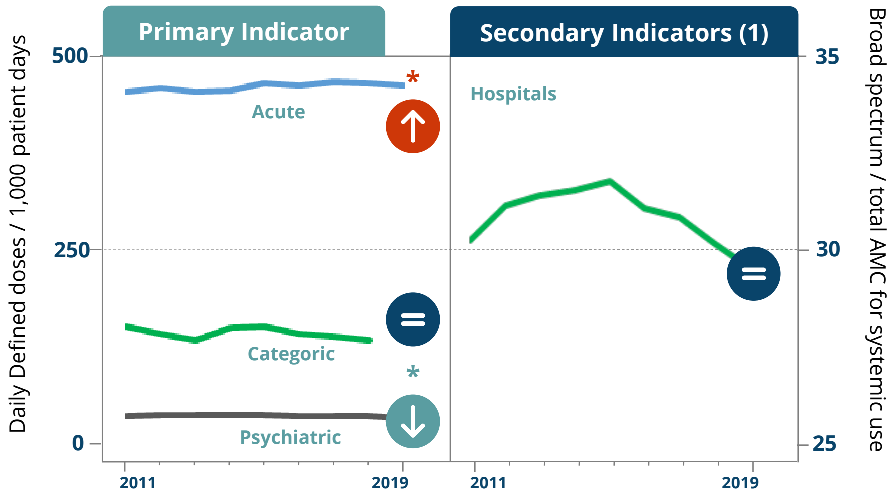
Humane sector

In het laatste decennium zagen we een afname van het gebruik van antimicrobiële middelen in de **ambulante sector**, met een cumulatieve reductie van 14% in de terugbetaalde antibiotica tussen 2010 en 2019. Tijdens de Covid-19 pandemie werd een sterke bijkomende reductie geobserveerd, wat kan gelinkt worden aan het aangepaste type van zorg tijdens de pandemie.

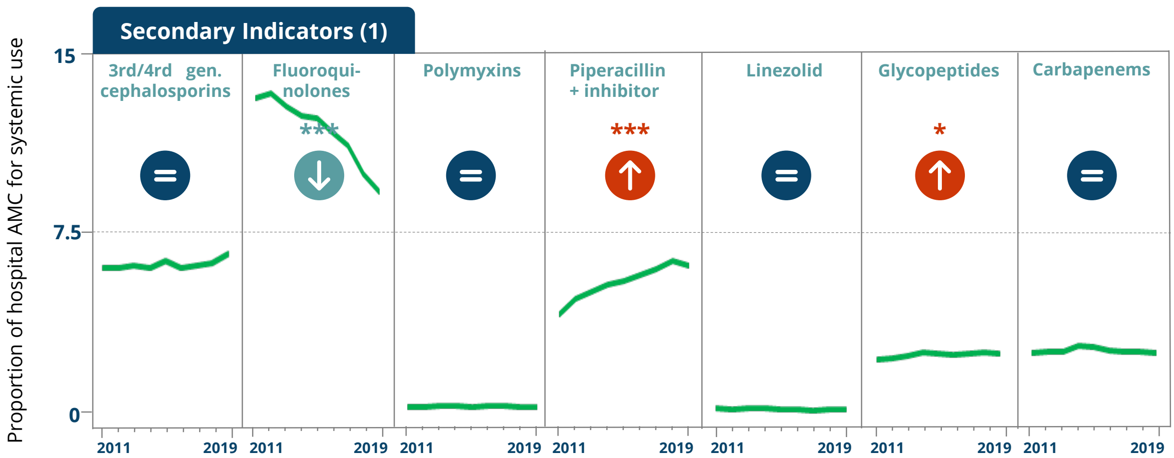


De verhouding in het gebruik van amoxicilline tot amoxicilline/clavulaanzuur verbeterde nauwelijks in het laatste decennium, van 46/54 in 2010 tot 51/49 in 2019, ver van de beoogde BAPCOC doelstelling van 80/20. Ook de reductie in het proportioneel gebruik van fluoroquinolones (5% in 2018) werd niet bereikt en bedroeg 6.7% in 2019, ook rekening houdend met de niet-terugbetaalde consumptie. Aan de positieve kant, daalde de verhouding tussen breed[8] -en eng-spectrum antibiotica wel significant.

In de **Belgische ziekenhuizen** voor acute zorg werden tussen 2011 en 2019 gemiddeld 450 'Defined Daily Doses' (DDDs) per 1000 zgn. patiëntendagen gebruikt, en dit gebruik steeg licht (3%) tijdens deze periode. Er bestaan grote verschillend tussen acute, categorische[9] en psychiatrische ziekenhuizen, en tussen primaire, secundaire en tertiaire ziekenhuizen. De proportie van breedspectrum antibioticagebruik in Belgische ziekenhuizen (29.5% in 2019) verbeterde licht maar niet significant. Ook deze parameter varieerde sterk, zoals kan gelezen worden in de rapporten van BeH-SAC.

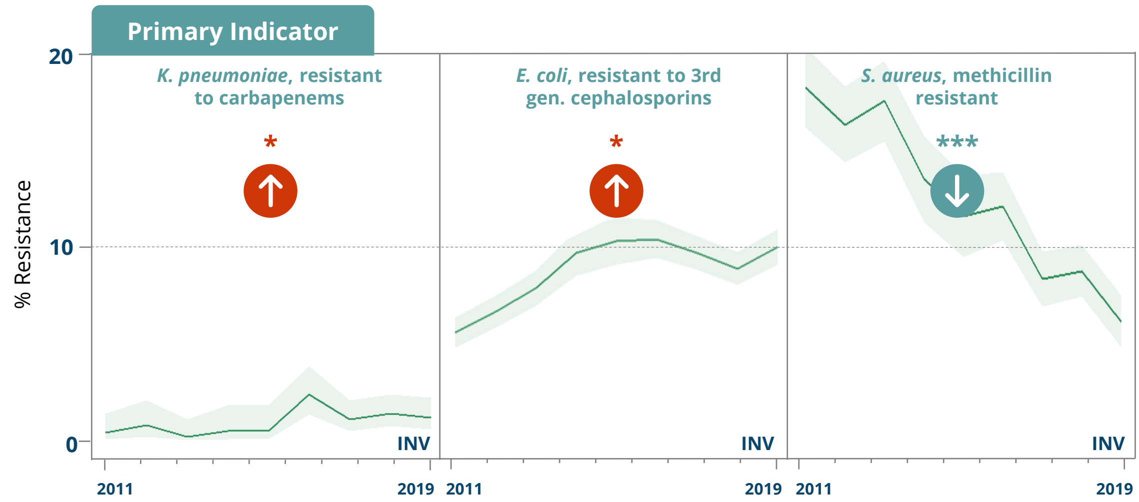


Er bestaan grote verschillen in de proporties van de verschillende breedspectrum antibiotica in het totale antibioticagebruik in ziekenhuizen. Een zeer significante daling van het aandeel van fluoroquinolones (-27% tussen 2011 en 2019) contrasteert met een toename van het gebruik van piperacillin in combinatie met tazobactam (+48%). De toename van het gebruik van glycopeptides (+12%) situeerde zich in de periode tussen 2011 en 2013.

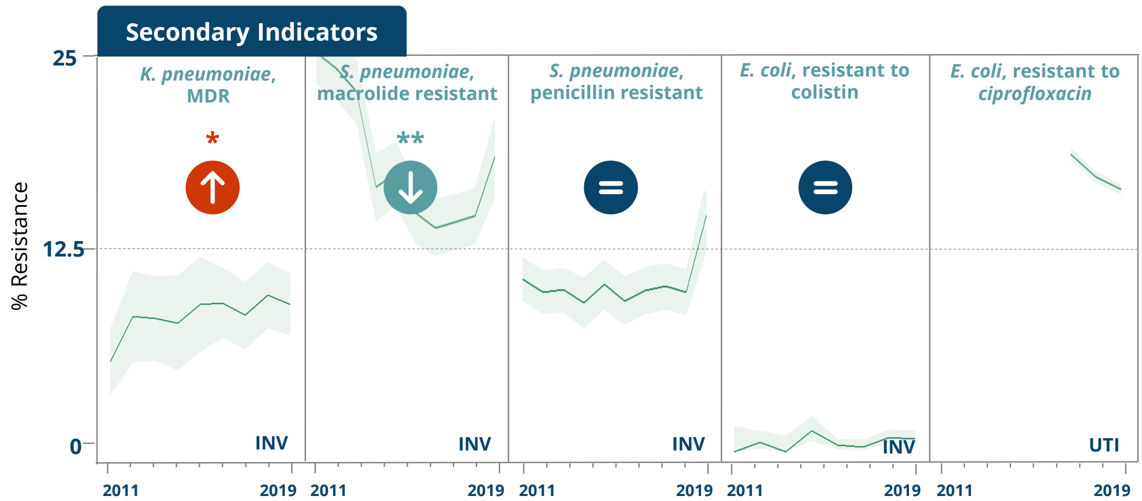


Bij humane pathogenen

BELMAP gebruikt licht gewijzigde indicatoren voor resistentie in humane pathogenen die in 2017 werden voorgesteld voor EMA en ECDC[1] , om meer aan te sluiten met de klinische realiteit. Zo werd de prevalentie van carbapenem-resistente *K. pneumoniae* opgenomen als primaire indicator, en werd ciprofloxacine resistentie in *Salmonella* en *Campylobacter spp.* verwijderd van de lijst met secundaire indicatoren.



INV: Bacterial isolates from clinical invasive samples (blood and cerebrospinal fluid)



UTI: Isolated from urinary tract infections. No trend analysis given limited data availability

In het laatste decennium nam de proportie van methicilline-resistente *Staphylococcus aureus* (MRSA) isolaten sterk en continu af in België. Dit contrasteert met een groeiende proportie aan invasieve E. coli isolaten resistent tegen 3de generatie cefalosporines, hoewel een stabilisatie rond 10% zichtbaar is vanaf 2014.

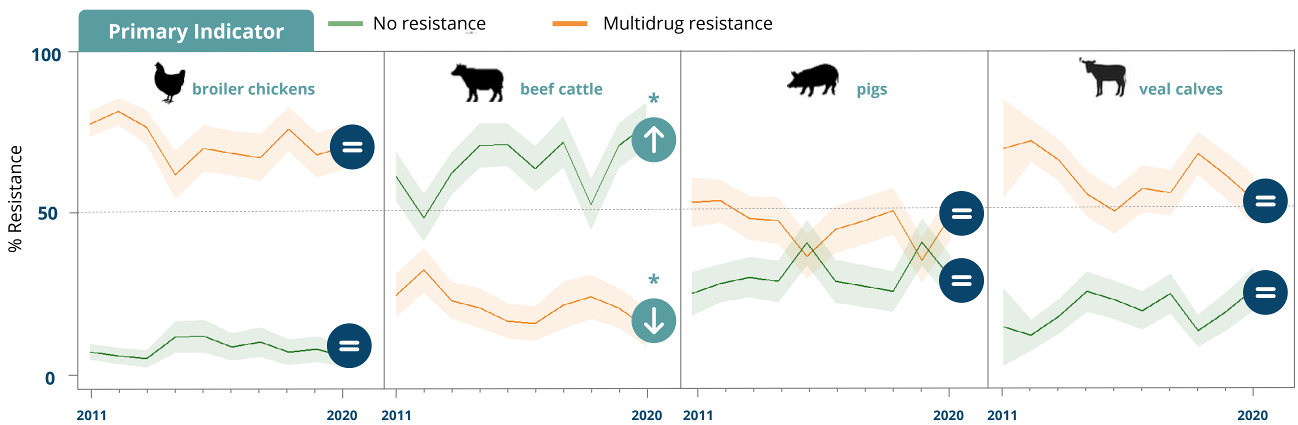
De prevalentie van carbapenem-resistente *K. pneumoniae* nam toe en bereikte 1.2% in 2019. De proportie van multi-drug resistente (MDR) *K. pneumoniae* resistent tegen 3de generatie cefalosporinen, aminoglycosides en fluoroquinolones nam licht toe (2011-2014) en stabiliseerde rond de 10%, hetgeen lager blijft dan het (dalende) Europese gemiddelde. De resistentie tegen colistine in invasieve *E. coli*, toegevoegd aan de indicatoren wegens het gebruik van dit antibioticum in humane als veterinaire sector, bleef onder de 1%.

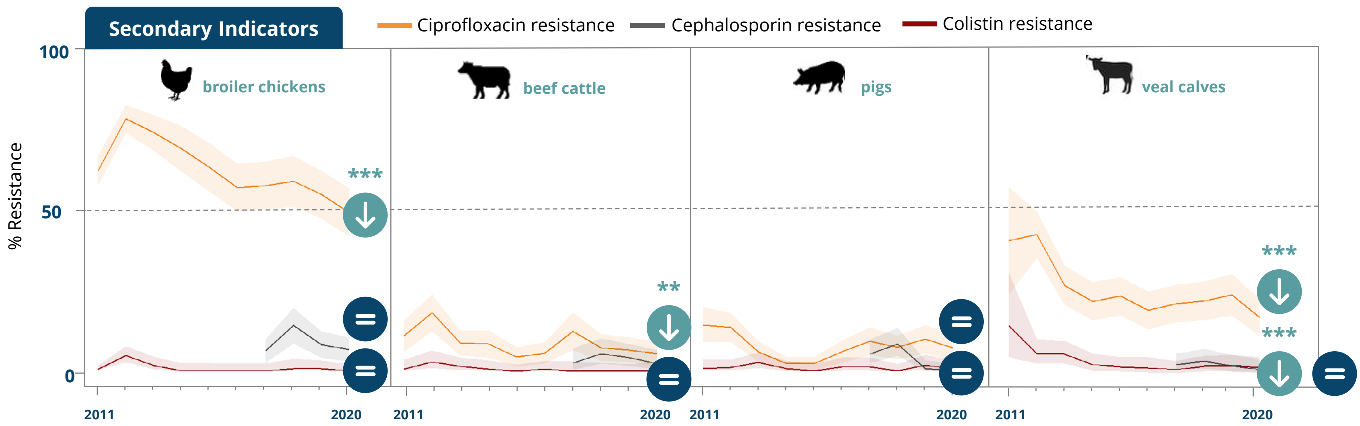
In 2020 werd een stijging van penicillineresistente vastgesteld in invasieve S. *pneumoniae* stammen, een scherp contrast met het voorgaande stabiele niveau van 10% (2011-2019). Dit zou kunnen veroorzaakt zijn door een aanpassing van de interpretatie van de gevoeligheidstest aan het referentiecentrum, en/of een substantiële reductie van het aantal geteste stammen in 2020 door COVID-19. Een zelfde trendbreuk werd vastgesteld voor macrolideresistentie, waar na een initiële afname van resistentie een stabiele resistentie van 15% werd gemeten tussen 2015 en 2019.

Bij commensale *E. coli* geïsoleerd uit gezonde voedsel-producerende dieren

In BELMAP worden gegevens gebruikt uit de monitoring van commensale *E. coli* geïsoleerd uit gezonde dieren, als indicator voor specifieke resistentieniveaus in de voedselproducerende dieren. *E. coli* is een zeer wijdverspreide bacterie die resistentiegenen kan opnemen van andere bacteriën in de omgeving, mens en dier. Het de huidige consensus dat de resistentieniveaus van *E. coli* een reflectie bieden van de selectiedruk van antibiotica in de bacteriële populatie.

Er bestaan grote verschillen tussen de dierengroepen. De hoogste proportie aan volledig gevoelige *E. coli* vindt men in runderen, waar significante stijging van de proportie pangevoelige stammen werd vastgesteld, tot een recordniveau van 78% in 2020. Gekoppeld hieraan is er ook een significante daling van het aantal MDR *E. coli* stammen. In geen van de drie andere dierenpopulaties waarin resistentie in *E. coli* wordt opgevolgd (vleeskuikens, varkens en kalveren) werden significante wijzigingen vastgesteld in de proportie van volledig gevoelige bacteriën (2011-2020). Het hoogste niveau van MDR *E. coli* wordt teruggevonden in pluimvee.





In zowel pluimvee, runderen als kalveren werd er bovendien een significante afname van ciprofloxacine resistentie vastgesteld (2011-2020), waarbij het laagste niveau ooit bereikt werd in 2020. Ook het niveau van colistine resistentie in vleeskalveren nam significant af. Voor de andere dierengroepen die gemonitord worden, bleef de prevalentie van resistentieniveaus tegen ciprofloxacine, colistine en cefalosporines stabiel op een laag niveau, nl. onder de 10%.

Vragen en opmerkingen op BELMAP 2021 :

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1 KURZFASSUNG

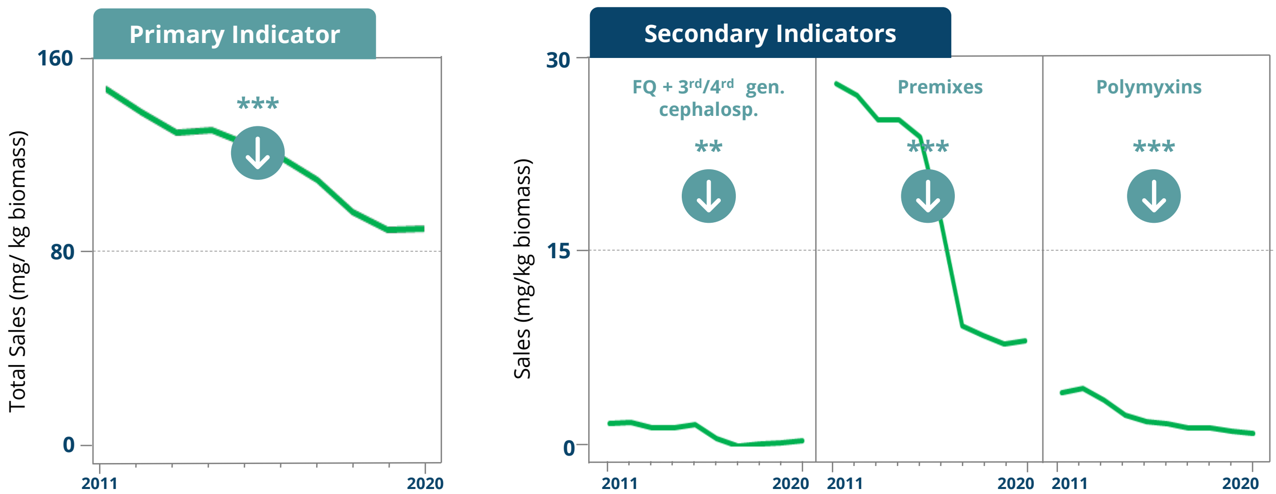
BELMAP verwendet Schlüsselindikatoren, um Trends beim Verbrauch antimikrobieller Mittel (AMC) und bei der antimikrobiellen Resistenz (AMR) bei Menschen und lebensmittelliefernden Tieren in Belgien zusammenzufassen. Die ausgewählten Indikatoren, die gegenüber den von ECDC, EFSA und EMA 2017 empfohlenen Indikatoren[1] leicht abgeändert wurden, sind in primäre und sekundäre Indikatoren unterteilt.

Die Primärindikatoren spiegeln im Großen und Ganzen die Situation in Bezug auf AMC und AMR wider. Sie decken nicht alle Aspekte der AMC- und AMR-Epidemiologie ab und bleiben willkürlich, können aber für eine **allgemeine Bewertung der Gesamtsituation** herangezogen werden. Sekundärindikatoren sollen Informationen über spezifischere Themen liefern, die auch für die öffentliche Gesundheit als wichtig erachtet werden, aber einen engeren Anwendungsbereich haben, oder Bereiche umfassen, die durch den Primärindikator nicht vollständig abgedeckt werden. Mit Ausnahme der vorgeschlagenen Indikatoren für die Antibiotikaresistenz beim Menschen sind die Indikatoren im Allgemeinen nicht geeignet, um die Auswirkungen gezielter Maßnahmen in einem bestimmten Sektor zu überwachen, z. B. in einer einzelnen Tierart oder einem Sektor der Tierproduktion[1].

ANTIMIKROBIELLER VERBRAUCH

Veterinärbereich

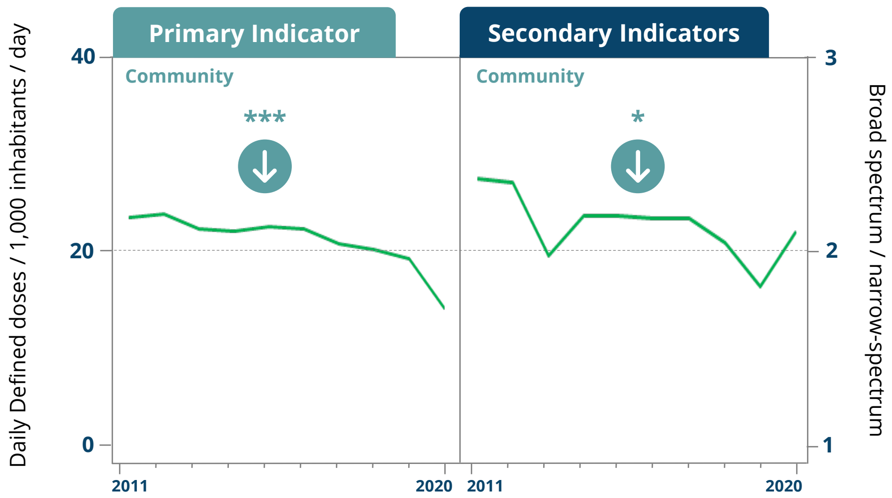
Der Verbrauch von antimikrobiellen Mitteln im Veterinärsektor, gemessen am Gesamtumsatz (mg/kg Biomasse), ist seit 2011 **stark zurückgegangen**. Die Daten zeigen einen kumulativen Rückgang von 40,2 % im Jahr 2020, wobei in den letzten Jahren ein leichter Anstieg zu verzeichnen war. Der Rückgang ist bei den sekundären Indikatoren noch deutlicher, da die kritischen Antibiotika (Fluorchinolone und Cephalosporine der 3. und 4. Generation) im Jahr 2020 einen kumulativen Rückgang von 70,1 % im Vergleich zu 2011 aufweisen. Ein ähnlicher Rückgang (71,3 %) wurde für Polymyxine erzielt, während antibakterielle Vormischungen im selben Zeitraum einen signifikanten kumulativen Rückgang von 70,4 % verzeichneten.



In Belgien wird seit 2018 der Einsatz von Antibiotika nach Sektoren und Tierkategorien erfasst und als BD100 oder als Prozentsatz der Zeit, in der ein Tier mit Antibiotika behandelt wird, ausgedrückt. Im gemessenen Zeitraum wurde eine signifikante Verringerung des BD100-Medians nur bei Kälbern erreicht. Dies ist jedoch nach wie vor der Sektor mit dem höchsten Antibiotikaeinsatz, dicht gefolgt vom Sektor der Absetzferkel.

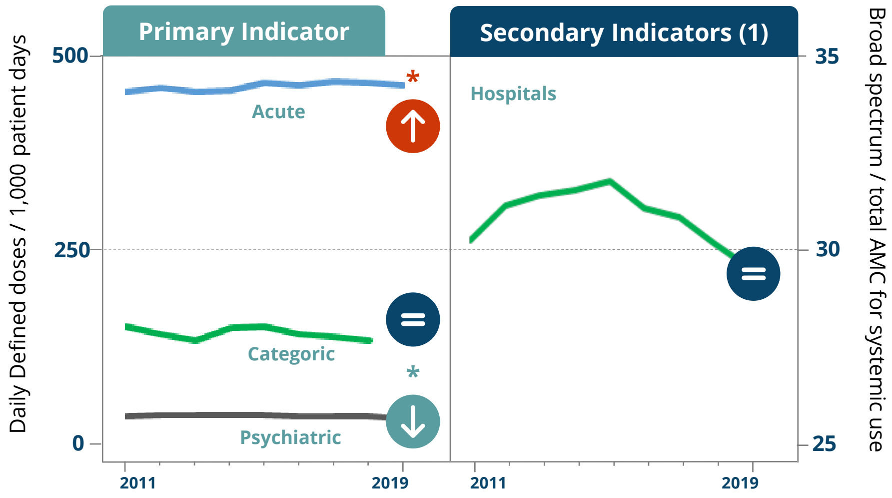
Humanbereich

In den letzten zehn Jahren ist der Einsatz antimikrobieller Mittel in der **Ambulanzmedizin / Gesellschaft** erheblich zurückgegangen. Von 2010 bis 2019 haben wir einen statistisch signifikanten Rückgang der erstatteten Antibiotika um 14 % festgestellt. Während der Covid-19-Pandemie wurde ein starker zusätzlicher Rückgang beobachtet, der mit den veränderten Versorgungsmustern während der Pandemie zu tun haben könnte.

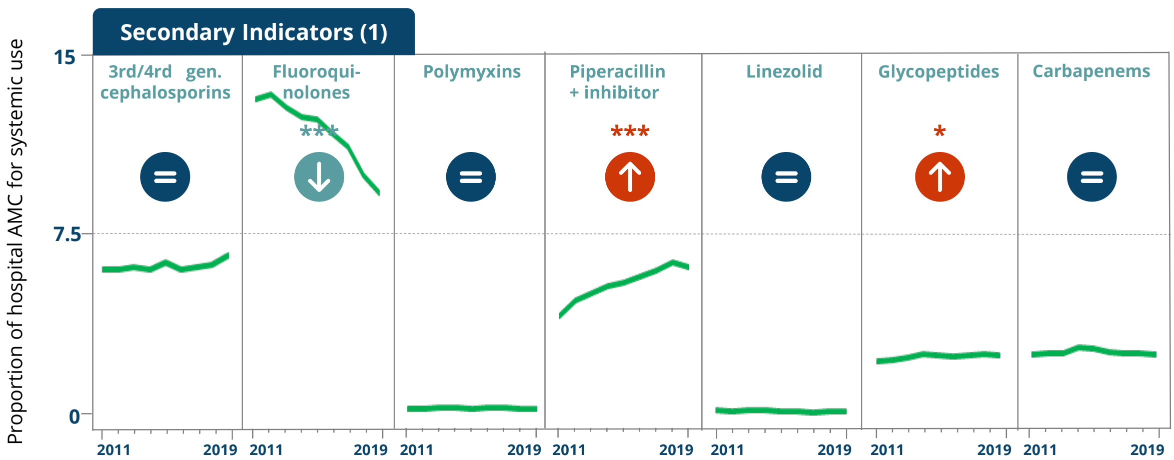


Das Verhältnis von Amoxicillin zu Amoxicillin/Clavulansäure hat sich in den letzten zehn Jahren nur leicht verbessert (von 46/54 im Jahr 2010 auf 51/49 im Jahr 2019) und ist immer noch weit vom BAPCOC-Ziel von 80/20 entfernt. Auch die angestrebte Verringerung des anteiligen Einsatzes von Fluorchinolonen (5 % im Jahr 2018) wurde nicht erreicht: 6,7 % im Jahr 2019, wobei der nicht erstattete Verbrauch berücksichtigt wird. Positiv zu vermerken ist, dass das Gesamtverhältnis von Breitspektrum[10]- zu Schmalbandantibiotika deutlich gesunken ist.

In den **belgischen Akutkrankenhäusern** (Daten 2011-2019) werden etwa 450 definierte Tagesdosen (DDDs) pro 1000 Patiententage erfasst, und dieser Verbrauch ist in den letzten zehn Jahren leicht gestiegen (3 %). Große Unterschiede bestehen zwischen Akutkrankenhäusern, Spezialkliniken/ Krankenhäusern für Chronisch Kranke[11] und psychiatrischen Krankenhäusern, auch im Vergleich nach Art des Krankenhauses (primär, sekundär, tertiär). Der Anteil des Breitspektrumeinsatzes in belgischen Krankenhäusern (29,5 % im Jahr 2019) hat sich im Laufe der Zeit nur leicht (aber nicht signifikant) verbessert. Auch für diesen Parameter wurde im BeH-SAC eine große Variation zwischen den Krankenhäusern gemeldet.



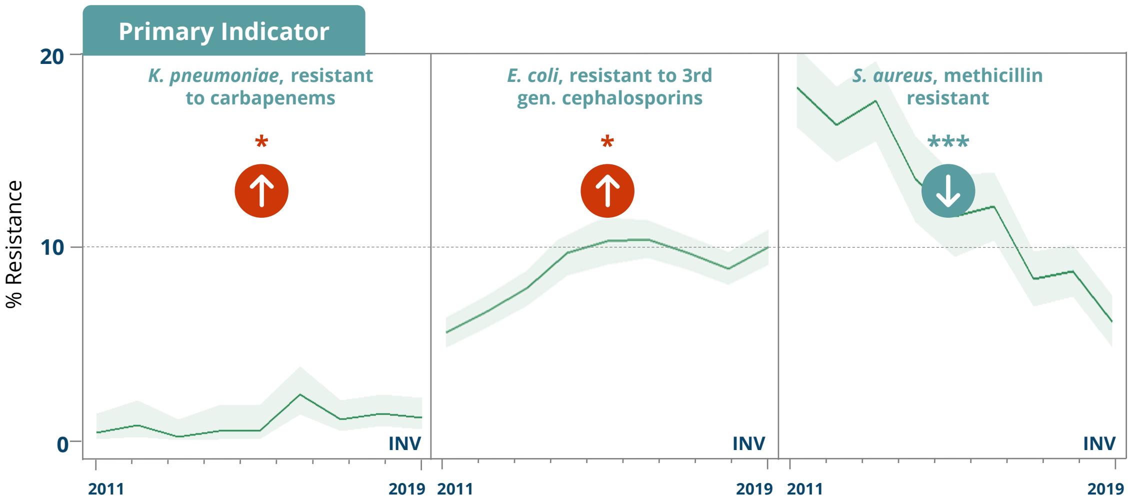
Betrachtet man den Anteil der Breitspektrum-Antibiotika an der gesamten Krankenhausverabreichung, so ist ein sehr deutlicher Rückgang bei der Verwendung von Fluorchinolonen zu beobachten (-27 % zwischen 2011 und 2019). Im Gegensatz dazu stieg der Anteil von Piperacillin in Kombination mit Tazobactam (+48 %) und Glykopeptiden (+12 %) im Laufe der Zeit deutlich an, obwohl der Anstieg der Verwendung von Glykopeptiden auf den Zeitraum 2011-2013 beschränkt war.



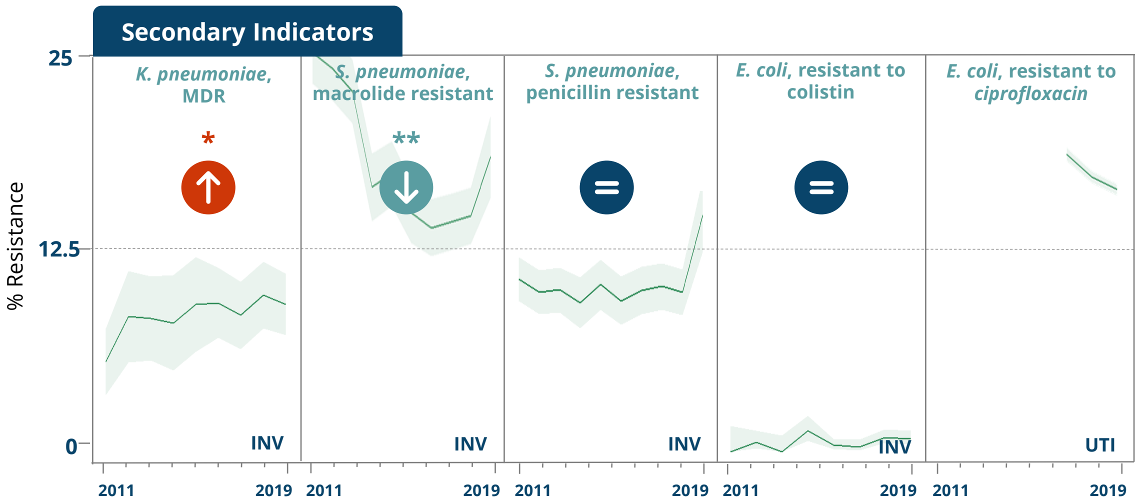
ANTIMIKROBIELLE RESISTENZ

Unter den menschlichen Krankheitserregern

BELMAP schlägt leichte Änderungen an den Schlüsselindikatoren für AMR bei Humanpathogenen vor, die 2017 von der EMA/ECDC[1] vorgeschlagen wurden. Die Prävalenz von Carbapenem-resistenten *K. pneumoniae* wurde als primärer Indikator priorisiert, und die Ciprofloxacin-Resistenz bei *Salmonella* und *Campylobacter spp.* wurde aus der Liste der sekundären Indikatoren entfernt.



INV: Bacterial isolates from clinical invasive samples (blood and cerebrospinal fluid)



UTI: Isolated from urinary tract infections. No trend analysis given limited data availability

In den letzten zehn Jahren ist der Anteil der Methicillin-resistenten *Staphylococcus aureus* (MRSA)-Isolate in Belgien stark und kontinuierlich zurückgegangen. Im Gegensatz dazu stieg der Anteil der klinischen *E. coli*-Isolate, die gegen Cephalosporine der 3. Generation resistent waren, obwohl nach 2014 eine Stabilisierung um 10 % zu beobachten war.

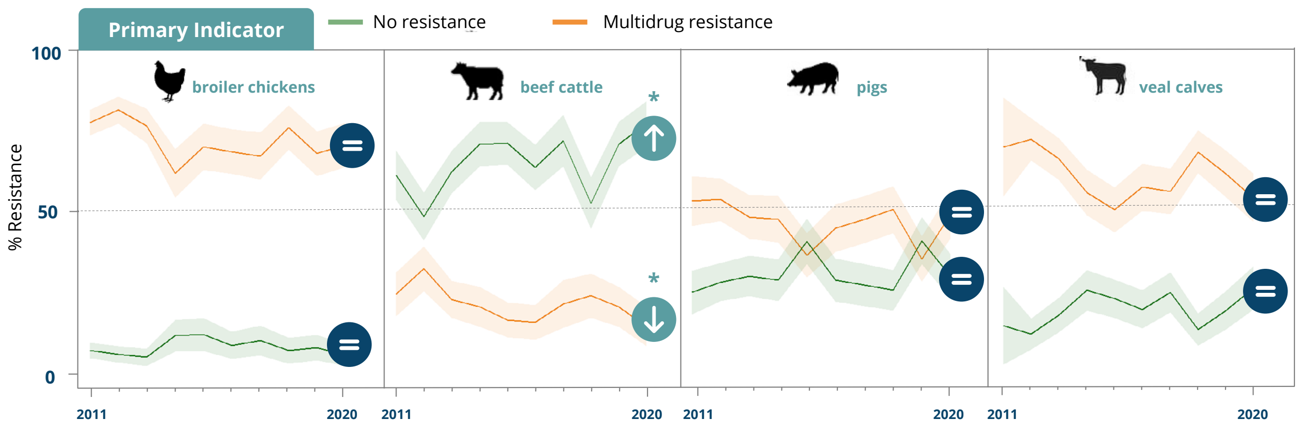
In den letzten zehn Jahren ist der Anteil der Methicillin-resistenten *Staphylococcus aureus* (MRSA)-Isolate in Belgien stark und kontinuierlich zurückgegangen. Im Gegensatz dazu stieg der Anteil der klinischen *E. coli*-Isolate, die gegen Cephalosporine der 3. Generation resistent waren, obwohl nach 2014 eine Stabilisierung um 10 % zu beobachten war. Die Prävalenz von Carbapenem-resistenten *K. pneumoniae* stieg in diesem Zeitraum leicht an und erreichte 2019 1,2 %. Der Anteil der multiresistenten (MDR) *K.-pneumoniae*-Stämme, die gegen Cephalosporine der 3. Generation, Aminoglykoside und Fluorchinolone resistent sind, stieg leicht an (2011-2014) und stabilisierte sich dann bei etwa 10 %, was im Vergleich zum (rückläufigen) europäischen Durchschnitt nach wie vor niedriger ist. Die Colistin-Resistenz bei pathogenen *E. coli*, die zu den Schlüsselindikatoren hinzugefügt wurde, um die Verwendung von Polymyxinen bei Mensch und Tier zu berücksichtigen, bleibt unter 1 %.

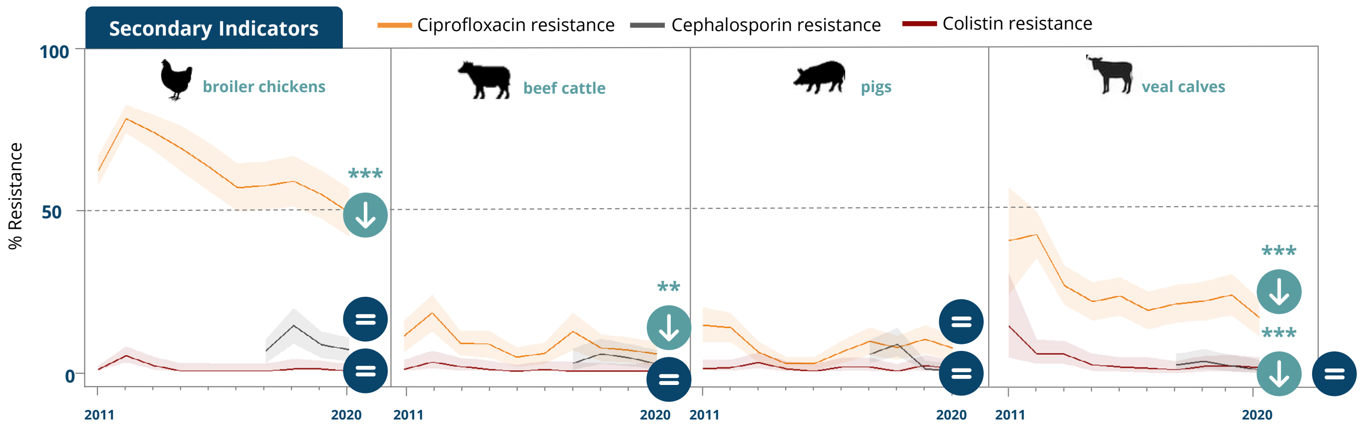
Im Jahr 2020 wurde eine Zunahme der Penicillin-Resistenz bei invasiven *S. pneumoniae*-Stämmen beobachtet, während die Penicillin-Resistenzrate von 10 % (2011-2019) stabil blieb. Dies könnte auf eine Umstellung bei der Interpretation der Ergebnisse von Empfindlichkeitstests im Nationalen Referenzzentrum (NRC) im Jahr 2019 und auf eine erhebliche Verringerung der Anzahl der gesammelten Proben im Jahr 2020 zurückzuführen sein. Bei den Makroliden war während der Covid-19-Krise ein ähnlicher Anstieg zu verzeichnen, dem ein anfänglicher Rückgang und eine stabile Resistenzrate von etwa 15 % im Zeitraum 2015-2019 gegenüberstanden.

Unter den Indikatoren, die von gesunden, der Lebensmittelgewinnung dienenden Tieren isoliert wurden

Da es keine öffentlich zugänglichen Daten über AMR bei Tierpathogenen gibt, verwendet BELMAP AMR-Daten zu Kommensalbakterien von gesunden Tieren als allgemeinen Indikator für Resistenzen bei Tieren, die der Lebensmittelerzeugung dienen. Sie können Resistenzgene von anderen Organismen in der Umwelt und in Tierpopulationen erwerben und bewahren. Daher spiegelt ihr Resistenzniveau das Ausmaß des Drucks wider, der durch Antibiotika in der Population ausgeübt wird.

Bei keiner der vier überwachten Populationen von Tieren, die zur Lebensmittelerzeugung genutzt werden (Masthühner, Rinder, Schweine und Kälber), sind signifikante Veränderungen des Anteils der vollständig empfänglichen *E. coli*-Stämme zu beobachten (2011-2020). Zwischen den Tiergruppen bestehen große Unterschiede. Der höchste Anteil an vollständig empfänglichen *E. coli*-Stämmen wird bei Rindern isoliert, mit einem Rekordwert von 78 % pansensibler Stämme im Jahr 2020. Der Anteil der multiresistenten *E. coli* ist bei Geflügel am höchsten und geht bei Geflügel und Rindern leicht zurück.





Sowohl bei Geflügel als auch bei Kälbern ist ein signifikanter Rückgang der Ciprofloxacin-Resistenz über den gesamten Zeitraum 2011-2020 zu beobachten, wobei die niedrigsten Werte im Jahr 2020 erreicht wurden. Ebenso ging das Auftreten von Colistin-Resistenzen bei Kälbern deutlich zurück. Bei allen anderen Tierarten blieb die Prävalenz der Ciprofloxacin-, Colistin- und Cephalosporin-Resistenz stabil und sehr niedrig, d. h. sie lag über die Jahre hinweg unter 10 %.

Fragen und Anmerkungen zu BELMAP 2021:

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2 INTRODUCTION

Since penicillin was first discovered in 1928, life-saving antimicrobials have revolutionized our society and economy. Previously deadly diseases have become routine illnesses, requiring little more than a brief treatment. These achievements are now at risk mainly because of the excessive or inappropriate use of antimicrobials, which has led to the increasing emergence and spread of multi-resistant bacteria. Without effective action to reverse current trends, we could face a return to the pre-antibiotic era, with simple wounds and infections causing significant harm and even death and routine medical procedures becoming very high risk. The threat is real, as every year 33,000 people die from an infection due to bacteria resistant to antibiotics in Europe. The burden of infections with bacterial resistance to antibiotics in the European population is comparable to that of influenza, tuberculosis and HIV/AIDS combined[12].

Antimicrobial resistance is a prime example of a 'One Health' issue. It is now widely recognized that human and animal health are interconnected, that diseases are transmitted from humans to animals and vice versa and must therefore be tackled in both. Also the environment is increasingly acknowledged as a contributor to the development and spread of AMR, in particular in high risk areas due to human, animal and manufacturing waste streams. Given the important and interdependent human, animal, and environmental dimensions of antimicrobial resistance, it is logical to take a One Health approach when addressing this problem.

ONE WORLD ONE HEALTH

A NATIONAL ACTION PLAN

The NAP-AMR has been developed to create more coherence and to set up a multisectoral cooperation mechanism and effective coordination between partners. It presents the common ambitions and brings together all the Belgian initiatives. The two central challenges of this plan are (i) to better prevent and control infections in order to reduce the transmission of micro-organisms and resistance between humans, animals and the environment as to minimize the need for antimicrobials and (ii) to ensure the prudent use of antimicrobials.

To meet these challenges, a global view of the Belgian situation is needed to evaluate the impact of the measures put in place and to be able to act accordingly. In Belgium, an effective surveillance of AMC and AMR has been in place for several years (**Figure 1**). However, it was difficult to have a clear overview of the evolution across sectors. Following the 'One Health' approach, the BELMAP report not only aims to present the main available data but also to allow an analysis of the association between consumption and resistance within and between the different sectors.

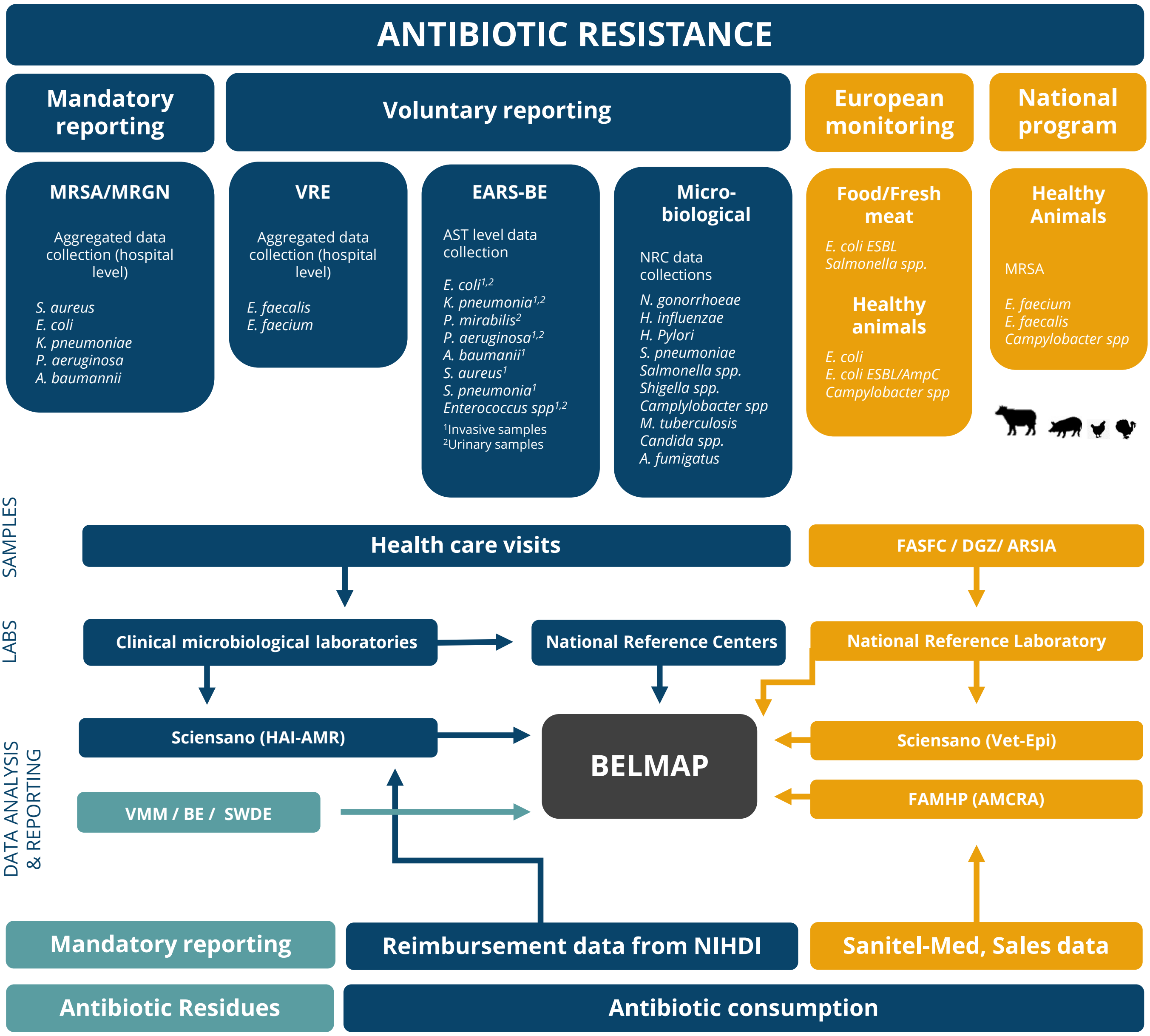

Figure 1. Overview of data flows used to generate the BELMAP 2021 report. Details are found in the following sections. MRSA, methicillin resistant Staphylococcus aureus; MRGN, multi-resistant Gram-negative bacteria; VRE, vancomycin resistant enterococci; NRC, National Reference Center, FASFC, Federal Agency for the Safety of the Food Chain; DGZ, DierenGezondheid Vlaanderen, ARSIA, l'Association Regionale de Santé et d'Identification Animales, NIHDI, National Institute for Health and Disability Insurance; HAI-AMR, Sciensano unit Hospital Acquired Infections and Antimicrobial Resistance; Vet-Epi, Sciensano unit Veterinary Epidemiology; VMM, Vlaamse Milieumaatschappij; BE, Brussels Environment; SWDE, Société Wallonne des Eaux. FAMHP, Federal Agency for Medicines and Health Products.

CLININAL AND EPIDEMIOLOGICAL BREAKPOINTS

Based on a recent survey among 117 clinical labs[13], 91.4% of all Belgian laboratories adhere to the guidelines of The European Committee on Antimicrobial Susceptibility Testing (EUCAST). This committee establishes breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing, and functions as the breakpoint committee of EMA and ECDC[14]. In this report, human antibiogram data was (for the majority of hospitals) interpreted according to EUCAST breakpoints which were valid in the year of reporting.

For indicator bacteria and food isolates, epidemiological cut-off values (ECOFF) are used which are specified in the dedicated sections. In this report, as in European reports, multidrug resistance (MDR) is defined as resistance to at least three different classes of antibiotics unless specified otherwise.

STATISTICAL ANALYSES

Line plots were generated in R (version R-3.6.3) using the ggplot2 package[15]. For each yearly observed proportion 95% confidence intervals (CI) were estimated using the asymptotic (Wald) method based on a normal approximation. In case of proportions close to 0% or 100%, the binomial (Clopper-Pearson) exact method was used to calculate 95% CIs. Confidence intervals were visualized using the geom_ribbon function of ggplot2 in R. We used a Log-linear poisson regression analysis to evaluate the effect of time (year) on the number of instances antimicrobial resistance occurred. An exposure variable (offset option in R) was included in the model to indicate the number of times resistance could have occurred in theory, i.e. sample size. In case of overdispersion, quasipoisson or negative binomial analyses were performed. A Spearman correlation test was performed to explore the relation between the consumption of antimicrobial agents and time. All statistical analyses were conducted in R. Results are indicated as *, ** and *** for results with p-values $0.05<p<0.01$, $0.01<p<0.001$ and $p<0.001$, respectively.

ABBREVIATIONS

Throughout the text, the following abbreviations are used:

3GC	3rd generation cephalosporins
AMC	Antimicrobial Consumption
AMU	Antimicrobial use
AMR	Antimicrobial Resistance
ARSIA	l'Association Régionale de Santé et d'Identification Animales
BAPCOC	Belgian Antibiotic Policy Coordination Committee
BD100	treatment days out of 100 days present at the farm
BeH-SAC	Belgian Hospitals - Surveillance of AMC
BelVet-SAC	Belgian Veterinary Surveillance of Antibacterial Consumption National consumption
CRKP	Carbapenem-resistant K. pneumoniae
CI	Confidence Interval
CRE	Carbapenem Resistant Enterbacterales
CPE	Carbapenemase Producing Enterbacterales
DDD	Defined Daily Dose
DGZ	DierenGezondheid Vlaanderen
DID	Defined Daily Dose per 1000 inhabitants per day
EARS-NET	European Antimicrobial Resistance Surveillance Network
ECDC	European Center for Disease Prevention and Control
ECOFF	epidemiological cut-off values
EFSA	European Food Safety Agency
EMA	European Medicines Agency
ESAC-Net	European Surveillance of AMC network

ESBL	Extended spectrum β-lactamase
ESVAC	European Surveillance of Veterinary Antibacterial Consumption
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAMHP	Federal Agency for Medicines and Health Products
FASFC	Federal Agency for the Safety of the Food Chain
FQL	Fluoroquinolones
HAI-AMR	Hospital Acquired Infections and Antimicrobial Resistance
MDR	Multidrug resistance
MRGN	multi-resistant Gram-negative bacteria
MRSA	Methicillin resistant Staphylococcus aureus
MSM	Men having sex with men
NIHDI	National Institute for Health and Disability Insurance
NTHi	non typeable Haemphilus influenzae
NRC	National Reference Center
PNEC	Predicted No Effect Concentrations
PPS	Point-prevalence study
SWDE	Société Wallonne des Eaux
VMM	Vlaamse Milieumaatschappij
VRE	Vancomycin resistant enterococci
WHO	World Health Organization

3 ANTIMICROBIAL CONSUMPTION IN HUMANS

3.1 METHODOLOGY

ESAC-Net (European Surveillance of Antimicrobial Consumption network) is the European network of national surveillance systems of antimicrobial consumption organized by ECDC. Based on a shared protocol, different European countries are collecting antimicrobial consumption data in the ambulant and/or hospital sector. This consumption is expressed in DDDs (Defined Daily Dose) per 1000 inhabitants per day (DID), using the country population as denominator[16]. For Belgium, reimbursement data from the National Institute for Health and Disability Insurance (NIHDI) are used in ESAC-Net. The data for the community include all antimicrobial packages delivered in community pharmacies (including all nursing homes who receive their medication from a community pharmacy, which is the majority in Belgium). Hospital data include all deliveries in hospital pharmacies.

Besides ESAC-Net, a more detailed national surveillance of antimicrobial consumption called BeH-SAC (Belgian Hospitals - Surveillance of Antimicrobial Consumption) was set up in Belgian hospitals, with the possibility to benchmark between hospitals. BeH-SAC is also based on reimbursement data of NIHDI. The antimicrobial consumption is expressed in DDDs/1000 patient days and DDDs/1000 admissions, using the hospital population as denominator. The presented data include inpatient wards (excluding outpatient wards and day hospitalizations)[17].

A consequence of using NIHDI data (in ESAC-Net and BeH-SAC) is that only reimbursed consumption is included. Non-reimbursed off-label use or imported antimicrobials agents are not considered, leading to a small but sometimes meaningful underestimation, notably as the use of new broad-spectrum antibiotics like cefiderocol might indicate the emergence of drug resistant organisms. Consumed units/packages per drug were translated in DDDs based on the DDD classification of the World Health Organization (WHO) Collaborating Centre for Drugs Statistics and Methodology (version December 2020)[18]. Administration routes that are included are oral, intravenous, intramuscular, subcutaneous, inhalation and rectal.

In addition to these surveillance, point-prevalence studies (PPS) of health-care associated infections and antimicrobial consumption are organized in hospitals and long-term care facilities on regular time points[19,20,21,22].In all these PPS studies, data were collected from each hospital ward or facility on one single day by a local data collector. The observed prevalence of patients/residents with at least one antimicrobial was calculated by dividing the number of patients/residents receiving at least one antimicrobial by the total number of eligible patients/residents. Observed prevalence are presented along with their 95% confidence intervals (95%CI). More information on the methodology of the different surveillances and studies can be found in the respective protocols and the latest national report of antimicrobial consumption in humans[23].

3.2 COMMUNITY[21,22]

The last decade has seen a considerable reduction in antimicrobial use in the community. From 2010 to 2019, we noted a statistical significant reduction of 14% in DID in reimbursed antibiotics (from 23.1 DID to 19.8 DID). During the Covid-19 pandemic, an additional reduction to 15.3 DIDs was observed (**Figure 2**). This may be due to the changed pattern of care during the pandemic, including fewer consultation by people suffering from flu and other (respiratory) infections that could otherwise have resulted in antibiotic prescriptions. EU data is only published in November 2021, hence it remains to be seen if this trend is common for all countries hit by Sars-CoV-2. Some countries that investigated the impact of the COVID-19 pandemic (Italy, Sweden, Portugal) already reported a reduction in overall antibiotic consumption in the community[24].

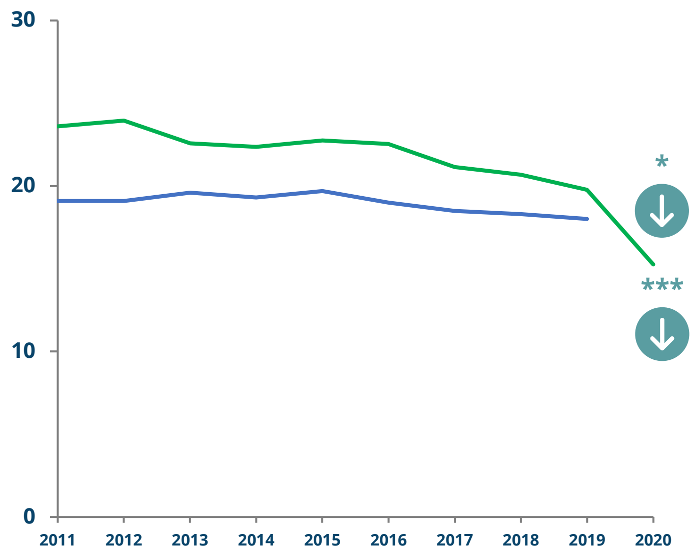

Figure 2. Consumption of antibacterials for systemic use (Defined Daily Dose per 1,000 inhabitants and per day, DID) in the community in Belgium (green), as compared to the EU mean (blue). For EU, no data point for 2020 at the time of writing. Data source: ESAC-Net.

According to the most recent reported data (2019)[21], the five most used products in the ambulant setting were amoxicillin, amoxicillin/clavulanic acid, nitrofurantoin, azithromycin and cefuroxime. In the last decade (2010-2019), an increase in consumption was seen for the classes macrolides and lincosamides. Decreasing trends were observed for fluoroquinolones, penicillins in combination with beta-lactamase inhibitors and 2nd generation cephalosporins. Since 2018, there was especially a large decrease in the reimbursed consumption of fluoroquinolones (but a substantial increase of non-reimbursed use[23]). A change in reimbursement criteria for fluoroquinolones starting from May 2018 onwards (reimbursement limited to a specific list of infections and conditions in the community[25]) coincided with this trend.

The ratio of amoxicillin to amoxicillin/clavulanic acid improved only slightly in the last decade (from 46/54 in 2010 to 51/49 in 2019), and is still far from the BAPCOC target of 80/20. Likewise, the targeted reduction in proportional use of fluoroquinolones (to 5% in 2018) was not reached: 6.7% in 2019, taking non-reimbursed consumption into account.

The ratio of broad-to narrow spectrum antibiotics declined ($p=0.04$) from 2.45 in 2011 to 1.93 in 2019, especially influenced by the decrease in reimbursed use of fluoroquinolones (**Figure 3**). This ratio is lower than the EU mean (2.84 in 2019), but there is a large range between countries (country range 0.1-20.1).

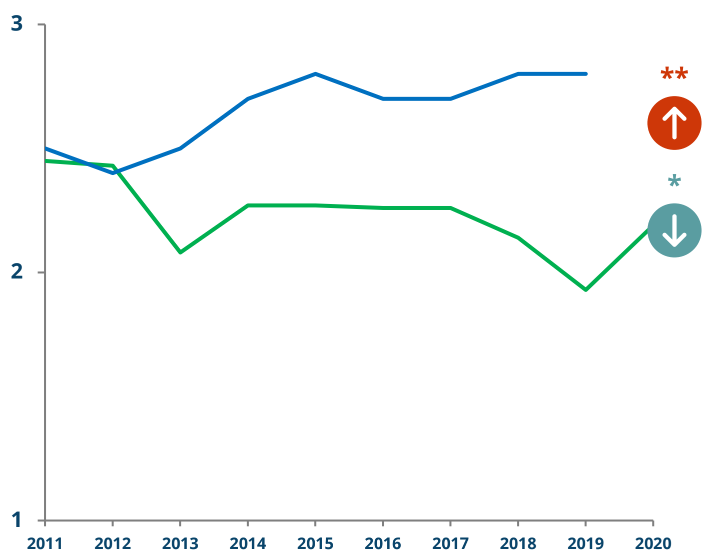

Figure 3. Ratio of broad-spectrum (penicillin, fluoroquinolones, macrolides and cephalosporins) to narrow-spectrum antibiotics for the community sector n Belgium (green) and EU (blue). Data source: ESAC-Net.

Notably, Belgium has a particular high usage of antimycotic and antifungal agents in the community setting. With 3.0 DID in 2019, we are among the highest consumers in the EU, which has a mean of 1.0 DID. Although a decrease in the last decade is seen, the antimycotic consumption in Belgium is still 3 to 6 times higher than our neighboring countries.

The last point prevalence study of antimicrobial prescription in nursing homes (HALT-3) dates back from 2016, and reported a small increase in the observed prevalence of residents with at least one antimicrobial prescription on the day of the study: from 4.3% (95%CI 4.0-4.7) in 2010 and 5.1% (95%CI 4.6-5.5) in 2013 to 5.6% (95%CI 5.2-5.9) in 2016. One-third (35.8%) of the prescriptions were for prophylactic use.

3.3 HOSPITALS [21,22]

In hospitals, if expressed in DDDs per 1000 inhabitants/day (DIDs), the overall (reimbursed) antibiotic consumption decreased 13% in the period from 2010 to 2019, and the observed 1.6 DID in 2019 is in line with the EU mean of 1.8 DID. Although the total consumption is larger than in The Netherlands, the consumption in DID is comparable with France, Sweden and Denmark.

To describe the antimicrobial selection pressure as targeted as possible, it is preferred to use the hospital population as denominator (BeH-SAC). As shown in **Figure 4** below, around 450 DDDs per 1000 patient days are recorded in the Belgian acute care hospitals and this situation is generally stable over the last decade. Of note, the tendency to shorten hospital stays in acute care hospitals is reflected by a small increase in DDDs/patient days (+3%, 457.8 in 2019), coupled by a significant decrease in DDDs/1000 admissions (-6%, 3276 in 2019). Large differences exist between acute, categorical[26] and psychiatric hospitals, also when compared per type of hospital (primary, secondary, tertiary).

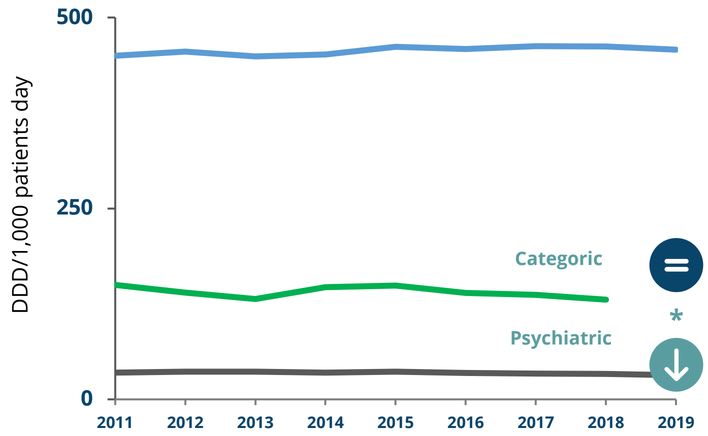

Figure 4. Consumption of antibacterials for systemic use (DDD per 1,000 patient days) in Belgian acute (blue), categorical (green) and psychiatric (grey) hospitals. Data source: ESAC-Net.

According to the most recent available data (2019)[21], the five most used products in acute hospitals (non-psychiatric inpatients wards) were amoxicillin/clavulanic acid, cefazolin, piperacillin/tazobactam, flucloxallin and ciprofloxacin. Between 2010 and 2019, the largest absolute increase in consumption was detected for the classes beta-lactamase resistant penicillins and penicillins with extended spectrum. The largest absolute decrease was seen for fluoroquinolones and penicillins in combination with beta-lactamase inhibitors. In contrast to the ambulant setting, the prescription of antimycotics and antifungals in all hospitals is overall in line with EU mean, and decreased significantly from 0.13 DIDs in 2010 to 0.10 DIDs in 2019.

The proportion of broad-spectrum use in all Belgian hospitals (29.5% in 2019) did only slightly (but not significantly) improve over time (**Figure 5**). Again, a high variation in this proportion between hospitals has been reported in BeH-SAC. In the EU countries which participated in the ECDC-PPS 2016-2017, the percentage of broad-spectrum antibiotic use in acute hospitals ranged from approximately 20% (Scotland, Lithuania) to more than 60% (Italy, Bulgaria)[27].

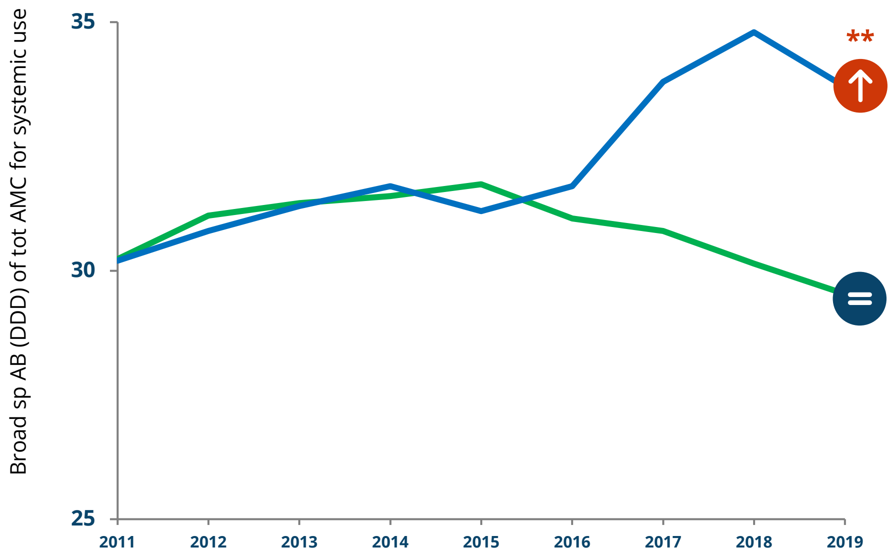

Figure 5. The proportion of broad-spectrum antibiotics (AB) (glycopeptides, third- and fourth-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitor, linezolid) out of total AB consumption (expressed in defined daily doses (DDD) per 1,000 inhabitants and per day in Belgian hospitals (green), as compared to the EU mean (blue). Data source: ESAC-Net.

Looking at the proportions of the different broad-spectrum classes, the largest, and very significant decrease is observed for the fluoroquinolones (-27% between 2011 and 2019). While the proportion of fluoroquinolones decreased, the proportion of piperacillin in combination with tazobactam (+48%) and glycopeptides (+12%) significantly increased over time (**Figure 6**).

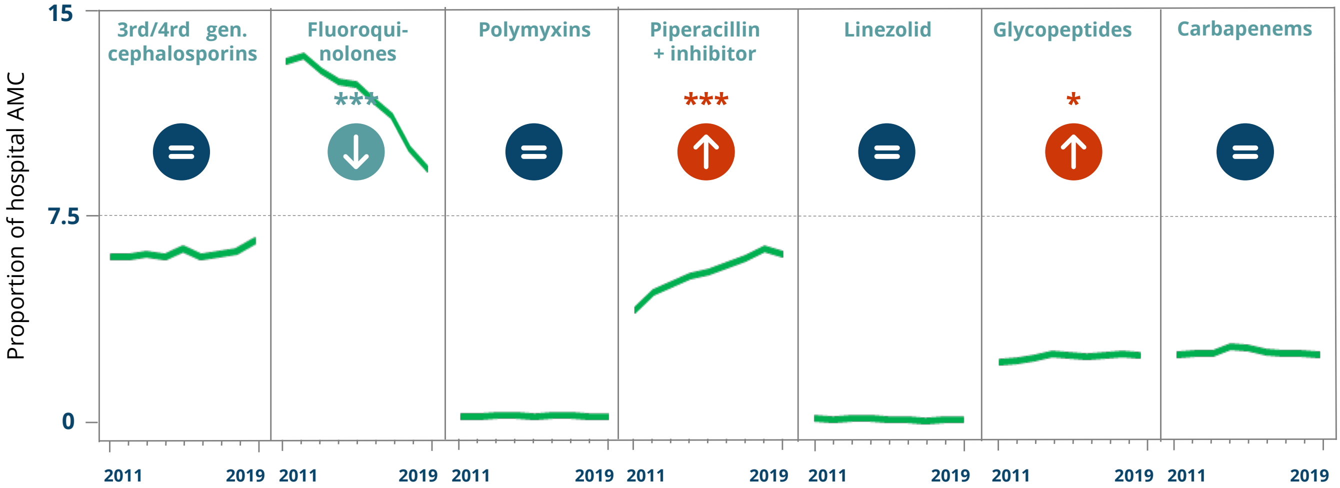

Figure 6. The proportion of third- and fourth-generation cephalosporins, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitor, linezolid, glycopeptides and carbapenems out of total antibiotics consumption (expressed in defined daily doses per 1,000 inhabitants and per day) in Belgian hospitals (green). For proportions source: ESAC-Net, all types of hospitals combined.

The last point prevalence study of antimicrobial prescription in acute hospitals dates from 2019 (Global-PPS), and reported 27.8% (95%CI 27.1-28.4) of patients with at least one prescription on the day of the PPS. In psychiatric hospitals in 2017, this prevalence was 3.8% (95%CI 3.2-4.3%).

4 ANTIMICROBIAL CONSUMPTION IN ANIMALS

4.1 METHODOLOGY

Data on antimicrobial use (AMU) in veterinary medicine is based on either sales data or delivery, prescription and administration data. Data on antibacterial sales in animals are published in the yearly Belgian Veterinary Surveillance of Antibacterial Consumption (BelVet-SAC) reports since 2007 (Belgian Veterinary Surveillance of Antibacterial Consumption, 2021). These data are collected at the level of the wholesaler-distributors and compound feed producers licensed to produce medicated feed and comprise all animal species. Details about the methodology of data collection and data analysis are provided in the BelVet-SAC report[28].

In addition to the sales data, use data at the farm-level are collected. Since 27 February 2017, veterinarians are legally obliged (RD of 21.07.2016) to register all antibacterial products (pharmaceuticals as well as premixes, incl. premixes containing ZnO as an antidiarrheal substance) prescribed, administered and delivered on Belgian farms with pigs, broilers, laying hens and veal calves in the secured online data collection system Sanitel-Med. The system, developed and maintained by the Federal Agency for Medicines and Health Products (FAMHP), is accessible as a web application or through automated data transfer using xml[29].

Since 2018, the BelVet-SAC report combines the sales data and farm-level use data, allowing to dig deeper into AMU at species and herd level in Belgium.

4.2 ANTIBIOTIC SALES

In veterinary medicine, sales data of the years 2011-2012 are used as reference years to follow reductions in antimicrobial use. Since 2011, total sales (mg/kg biomass) significantly decreased with a cumulative reduction of 40.2% in 2020 (**Figure 7**).

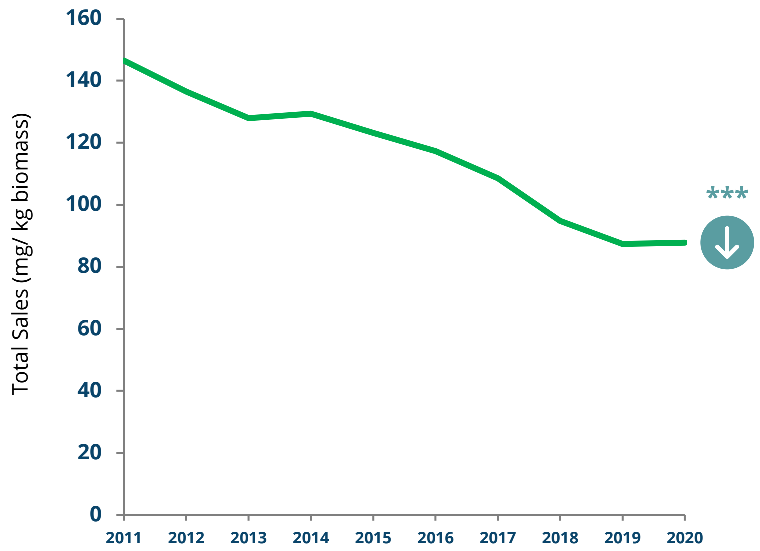

Figure 7. Evolution of the total antibacterial sales in the animal sector, expressed by mg/kg biomass. Source: BelVet-SAC reports.

Critically important antibiotics (fluoro)quinolones and cephalosporines of 3rd and 4th generation) had a cumulative reduction of 70.1% in 2020 compared to 2011, while the sales data of polymyxins showed a significant cumulative reduction of 71.3% in 2020 compared to 2012 (**Figure 8**). Likewise, antibacterial premixes had a significant cumulative reduction of 70.4% in 2020 compared to 2011.

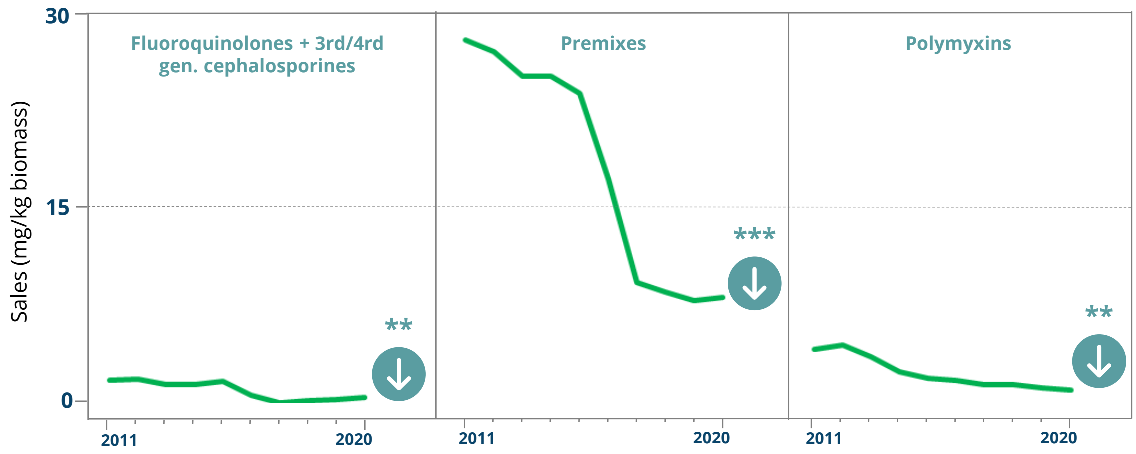

Figure 8. Evolution of the sales of fluoroquinolones+3rd/4rd generation cephalosporins, antibacterial premixes and polymyxins in the animal sector (2011-2020), expressed by mg/kg biomass. Source: BelVet-SAC reports.

4.3 ANTIBIOTIC USE

Comparison of the Sanitel-Med use data with the sales data in 2020 shows that almost 80% of total sales (in tonnes) in all animals was covered by the use in the three species, with pigs by far being the species where the largest mass of antibiotics was used (**Table 1**). Some antibiotic classes appear to be predominantly used in these three species, for example macrolides, polymyxins, tetracyclines and penicillins, while cephalosporins are mostly used in other species. Half of (fluoro)quinolones is used in these species, predominantly in poultry (and more specifically in broilers).

Tabel 1. Table 1. Total tonnes per antibacterial class sold in 2020 (Sales 2020) and total tonnes used in pigs, poultry and veal calves (Use 2020). Next to the tonnes used by each species the % this covers of the sales data (% sales) is shown. Source: BelVet-SAC report[23].

	Sales 2020	Use 2020							
	Tonne	Tonne Total	% sales	Pig tonne	% sales	Poultry tonne	% sales	Veal tonne	% sales
Penicillins	73,4	60,9	83	47,2	64	9,1	12	4,6	6
Tetracyclines	35,8	30,1	84	23,5	66	1,5	4	5,1	14
Trim-sulpha	35,4	21,6	61	16,4	46	4,4	12	0,8	2
Macrolides	18,2	17,8	98	7,2	40	6,3	35	4,2	23
Aminosides	9,2	7,1	79	3,1	34	2,7	30	1,3	14
Phenicols	3,3	1,9	57	1,6	50	<0,1	1	0,2	7
Polymixins	2,8	2,4	86	2,1	75	0,3	10	<0,1	1
Cephalosporins	1,4	0,0	1	0,0	1	0	0	<0,1	<1
Quinolones	1,4	0,7	49	0,0	<1	0,6	46	<0,1	3
Other	1,0	0,6	60	0,6	60	0	0	0	0

At sector and animal category level, use is expressed as BD100: the number of treatment days (with antibiotics) out of 100 days present at the farm, hence the percentage of time an animal is treated with antibiotics.

Figure 9. Median BD100 for the animal categories (sucklers, weaners, fatteners, breeding pigs, broilers, laying hens and veal calves) for which data are available in Sanitel-Med. Given only three datapoint, no statistical analysis was performed. Data range: 2018-2020.

Based on the yearly-average BD_{100}-values of the farms in the benchmark reference population per animal category, the distribution of the use in each animal category is followed. These distributions currently are all skewed with a long tail of high-using farms. In **Figure 9**, the evolution between 2018 and 2020 of the median BD_{100} from each animal category distribution is shown. Despite downward trends in fatteners and broilers, only the reduction achieved in veal calves appears to be significant over this short period of time. However, this remains the sector with the highest antibiotic use, closely followed by the category of the weaners in pigs.

5 ANTIMICROBIAL RESISTANCE IN HUMAN PATHOGENS

In 2017, the World Health Organization (WHO) published its first ever list of antibiotic-resistant "priority pathogens"[30]. The most critical group of all includes multidrug resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters. They include Acinetobacter, Pseudomonas and various Enterobacterales (including *Klebsiella spp.* and *E. coli*). They can cause severe and often deadly infections such as bloodstream infections and healthcare-associated pneumonia. The second and third tiers in the list – the high and medium priority categories – contain other increasingly drug-resistant bacteria that are in majority responsible for community-acquired infectious diseases such as gonorrhea and food poisoning. An update of this list is expected in 2022.

In BELMAP 2021, we present available AMR data on these pathogens for the 2011-2020 time period, and expand to other difficult-to-treat infections, including those caused by *Candida spp.* and *Mycobacterium tuberculosis*.

5.1 METHODOLOGY

Two different systems are in place for epidemiological monitoring of AMR in humans in Belgium:

- the Belgian national surveillances of methicillin resistant *Staphylococcus aureus* ("MRSA"), multi-resistant Gram-negative bacteria ("MRGN"), and vancomycin resistant enterococci ("VRE").

- the European (EU) Antimicrobial Resistance Surveillance Network for Belgium ("EARS-BE").

The MRSA, MRGN and VRE surveillances are the main **national surveillances** for antimicrobial susceptibility evolutions and incidence of multidrug resistant organisms in Belgium. By Royal Decree, acute care hospitals mandatorily have to participate in the MRSA and MRGN surveillances. Participation in the VRE surveillance is currently optional (Belgian Royal Decree of 25 April 2002). Data are collected retrospectively (year -1) and aggregated at hospital level. The AMR surveillance protocol is defined by the 'Healthcare-associated infections and antimicrobial resistance service' (HAI-AMR) of Sciensano, in collaboration with the relevant national reference laboratories (NRCs). For more information about this surveillance including the protocols and the reports from previous years, the reader is referred to the webpage of NSIH[31].

EARS-Net is the main **EU epidemiologic surveillance** system for AMR, and its data serve as important indicators on the occurrence and spread of AMR in European countries[32]. On a yearly basis, this monitoring system collects and reports across European countries data on AMR against relevant agents within commonly occurring pathogens isolated from clinical invasive samples (blood and cerebrospinal fluid (CSF)) in humans.

EARS-Net performs surveillance of seven bacterial pathogens commonly causing infections in humans: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter* species, *S. pneumoniae*, *S. aureus, E. faecalis* and *E. faecium*. EU member states are requested to participate to EARS-Net through EU recommendation (Council Recommendation, 2009/C 151/01).

National data collection and submission to EU for Belgium (BE) is also organized by the 'Healthcare-associated infections and antimicrobial resistance service' of Sciensano, and this by means of the so-called "EARS-BE surveillance". EARS-BE differs from EARS-Net in three major points : (1) the additional collection of antimicrobial susceptibility tests (AST) on isolates collected from urine (next to blood/CSF samples); (2) the inclusion of the pathogen *Proteus mirabilis*, a frequent cause of urinary tract infections ; (3) the distinction between all *Acinetobacter* species and the pathogen *A. baumannii*, the predominant species of the genus comprised in the ESKAPE pathogens commonly associated with antimicrobial resistance. Data are collected retrospectively (year - 1) and participation is voluntary. Microbiology laboratories are asked to specify data up to the level of individual combinations of the antimicrobial test and to transfer this file to Sciensano. The data call, case, data definitions and reports from previous years are available on the NISH website.

Apart from this resistance surveillance with aggregated data, clinical laboratories can voluntarily send isolates to National Reference Centers (NRCs) for phenotypic and genotypic characterization (including resistance profiles and confirmation of relevant resistance mechanisms) and/or molecular typing. These NRCs publish annual reports[33], from which data on resistance was extracted in this report.

5.2 INVASIVE INFECTIONS

Bloodstream infections (BSIs) are among the most severe clinical syndromes, and are considered a leading cause of unfaithful outcomes, increasing treatment costs and length of hospital stay. BSIs are one of the most frequent lethal conditions that are managed in intensive care units (ICUs), and require immediate antimicrobial therapy.

5.2.1 *Escherichia coli*

Escherichia coli is part of the commensal intestinal flora, but is also the most common pathogen in BSIs in Belgium, being isolated in 21% of the hospital-associated BSIs (HABSIs) in 2019[34]. The source of E. coli are most often urinary tract or abdominal infections. A major change in the its global epidemiology has been the emergence of resistance to 3rd generation cephalosporins (3GC) primarily caused by extended spectrum β-lactamase (ESBL) especially of CTX-M family. Another major event is the global spread of one very successful clone (ST131) that has emerged over the last two decades[35].

In Belgium, we have seen an increase in resistance to 3GC among *E. coli* isolated from BSIs (2011-2014), but this trend stabilized in the last years and reached 10.1% (427/4230 tested isolates) in 2019 (**Figure 10**). These levels are lower than EU averages (13.5% in 2019), and still much lower than in other parts of the world where levels up to 40% are recorded[36]. As for now, resistance to carbapenems and colistin among invasive *E. coli* isolates remains low (<1%)[37]. Of note, since 2017 the EARS-BE monitoring collects data on *E. coli* and *Proteus mirabilis* from urinary tract infections (UTIs). Ciprofloxacin resistance in *E. coli* from UTI decreased from 18.1% in 2017 to 15.9% in 2019, which mirrors the trend observed in invasive isolates in the same time period.

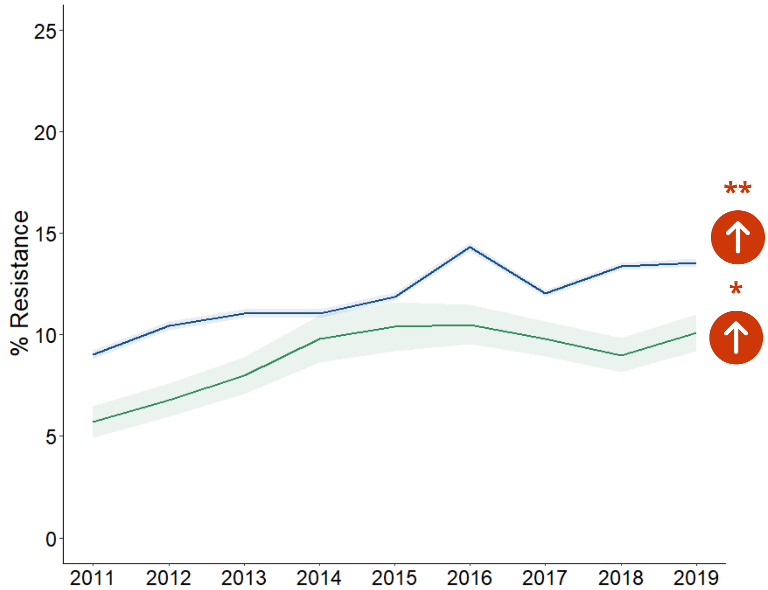

Figure 10. Proportion of invasive clinical isolates of *E. coli* isolated in Belgium (green) and resistant to 3rd generation cephalosporin, in comparison to EU averages labeled in blue. Source: EARS-BE data and ECDC's Surveillance Atlas of Infectious Diseases.

5.2.2 *Klebsiella pneumoniae*

Klebsiella pneumoniae can cause numerous nosocomial and community acquired acute or persistent invasive infections at different body sites. Globally, carbapenem-resistant *K. pneumoniae* (CRKP) has become one of bacterial pathogens with the highest impact on public health, accounting in Europe alone, for >90,000 infections and >7,000 deaths annually[38]. CRKP are especially of concern because of their epidemic potential causing major nosocomial outbreaks through dissemination of high-risk clones (e.g. clonal complex ST258), but also because of the risk on horizontal transfer of mobile genetic elements carrying carbapenemase genes, including plasmids (e.g. pOXA-48a plasmid)[39].

In Belgium, *K. pneumoniae* was isolated in 8% of HABSIs in 2019, making it the second most frequent Enterobacterales species. **Figure 11** shows the evolution of resistance in clinical isolates in 2011-2019. The prevalence of CRKP over this time period increased statistically significant, and reached 1.2% (10/822 tested isolates) in 2019.

Of note, **budgetary limitations hinder detailed molecular surveillance** on carbapenem resistant bacteria with no systematic microbiological and molecular surveillance of CRKP isolates in place. Therefore, the proportion of CPE (carbapenemase producers) among CRE (carbapenem resistant) is currently unknown, as is the distribution of the different carbapenemase family types within the CPE in BSI isolates.

The proportion of multi-drug resistant (MDR) *K. pneumoniae* strains resistant to 3GCs, aminoglycosides and FQLs increased substantially in 2012 and incrementally in the 2012-2019 period to 10% (**Figure 11b**), which is considerable lower compared to the (declining) European mean. However, one must take into account the strong variation in CRKP prevalence among.

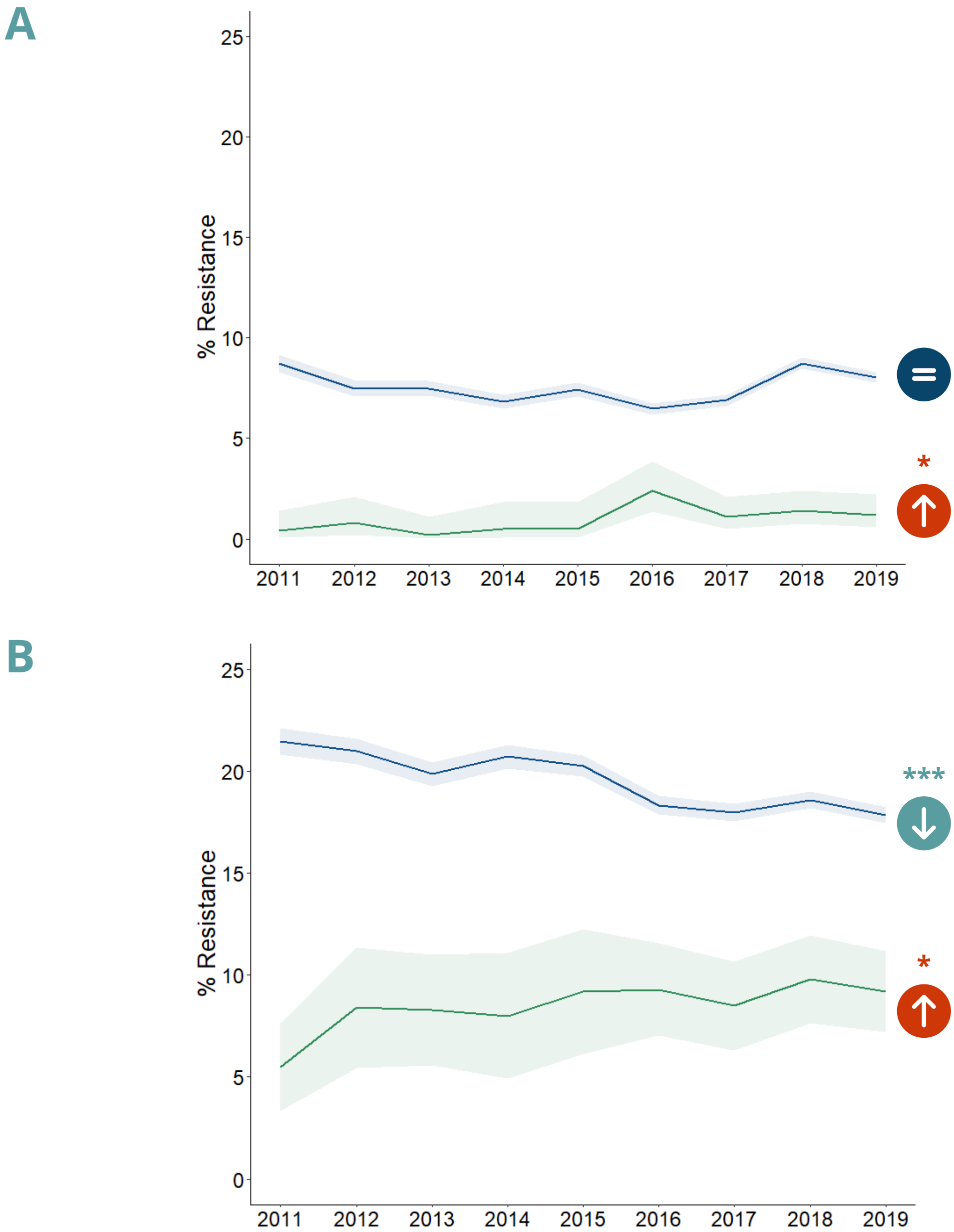

Figure 11. Proportion of invasive clinical isolates of K. pneumoniae isolated in Belgium (green) and the EU (blue) and resistant to (A) carbapenem and (B) a combination of aminoglycosides, fluoroquinolones and 3rd generation cephalosporins. Source: EARS-BE data and ECDC's Surveillance Atlas of Infectious Diseases.

5.2.3 *Acinetobacter spp.*

Acinetobacter spp. are ubiquitous in nature, and can spread to healthcare facility environment given their ability to persist on inanimate surfaces. By its higher virulence and intrinsic resistance to many antimicrobials, *A. baumannii* is the principal opportunistic pathogens species that can cause severe nosocomial infections most often in patients under intensive cares, such as pneumonia (often ventilator-associated), central-line associated bloodstream and urinary tract infections[40]. Immune suppression, invasive procedures, burns and traumatic wounds and extended hospital stay are some of the risk factors for *Acinetobacter* infections[41]. The environmental persistence of *A. baumannii* increases the difficulty of their elimination and eases transmission that can lead to difficult-to-control outbreaks. Due to historical difficulties in clinical labs to correctly identify *Acinetobacter* isolates to species level, the EARS-Net surveillance monitors the antimicrobial resistance of *Acinetobacter spp.* In addition to these results, since 2018, EARS-BE collected AST results on the subgroup of *A. baumannii* species.

Although often MDR, *Acinetobacter spp.* infections are uncommon and identified in <1% HABSIs in Belgian patients. Among the 134 and 67 *Acinetobacter spp* isolates included in the surveillance in 2018 and 2019, only 31 (23.1%) and 14 (20.9%) were identified as *Acinetobacter baumannii* species respectively. **Figure 12** shows the evolution of the carbapenem resistance among *Acinetobacter spp.* Given the low number of isolates, it remains difficult to obtain precise estimation of resistance prevalence at a national level. For future reports, data on the proportion of hospitals reporting (outbreaks of) carbapenemase producing *A. baumannii* and *P. aeruginosa* isolates will be available. In any case, the low prevalence in Belgium contrasts sharply with (declining) EU means, which are strongly influenced by soaring numbers of carbapenemase producing *A. baumannii* in Italy and Greece.

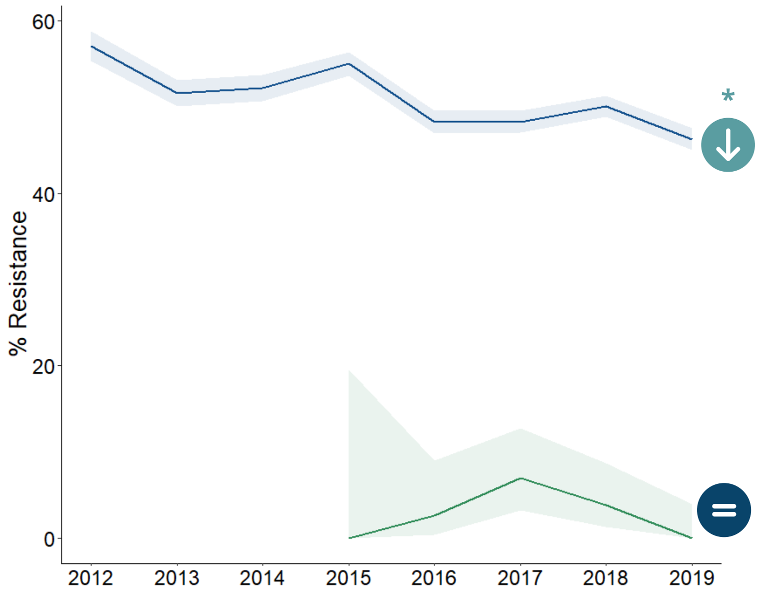

Figure 12. Proportion of invasive clinical isolates of Acinetobacter spp. isolated in Belgium (green) and resistant to carbapenem, in comparison to EU averages labeled in blue. Source: EARS-BE data and ECDC's Surveillance Atlas of Infectious Diseases.

5.2.4 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is commonly found in aquatic environments in nature. It is an opportunistic pathogen and a common cause of healthcare-associated pneumonia (including ventilator-associated pneumonia), bloodstream infections and urinary tract infections. In Belgium, *P. aeruginosa* was isolated in 4.9% of HABSIs in 2019. *P. aeruginosa* displays high intrinsic resistance to a large number of antimicrobial agents and has a high propensity to acquire and cumulate easily resistance mechanisms (chromosomal mutations and/or mobile elements horizontal transfer) resulting in multidrug-resistant phenotypes towards different antibiotics classes[42].

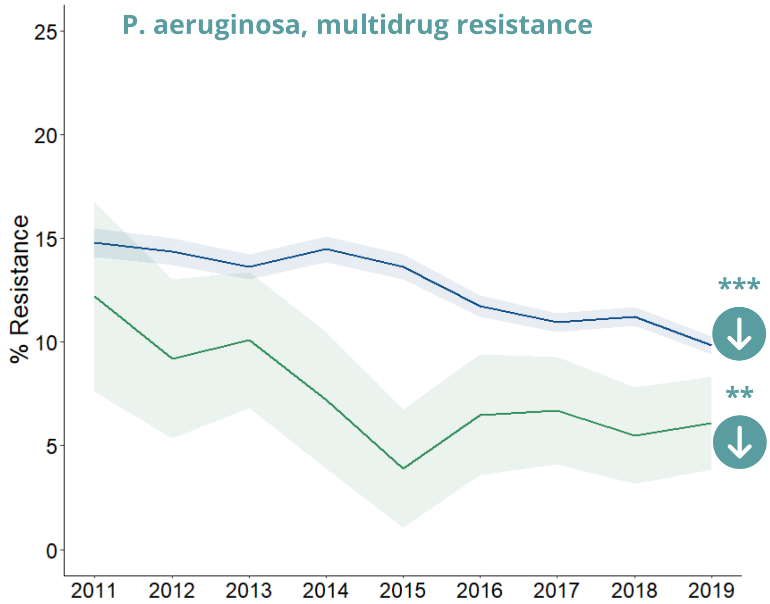

Figure 13. Proportion of invasive clinical isolates of P. aeruginosa isolated in Belgium (green) and resistant to at least 3 out of 5 AB groups (piperacillin-tazobactam, carbapenems, aminoglycosides, fluoroquinolones), in comparison to EU averages labeled in blue. Source: EARS-BE data and ECDC's Surveillance Atlas of Infectious Diseases.

Figure 13 displays the evolution of multi-drug resistance within invasive clinical isolates of P. aeruginosa from 2011 to 2019. Both the Belgian and European proportion of CRPA has declined significantly, although stabilization around 6% is observed in Belgium since 2014. Carbapenem resistant P. aeruginosa has a stable prevalence of approx. 10% in Belgium, which is comparable to our neighboring countries.

5.2.5 *Staphylococcus aureus*

Staphylococcus aureus usually is a commensal bacterium that commonly colonizes the skin of healthy humans. However, it can also become an opportunistic pathogen, being a common cause of skin, soft tissue and bone infections. It is also one of the leading cause of bloodstream infections in Europe[43]. The 2017 Belgian Point prevalence survey of healthcare-associated infections and antimicrobial use (PPS) estimated that 8.9% of healthcare-associated infections (HAI) were caused by *S. aureus*. That makes it the 2nd most often isolated pathogen from HAI in Belgium, as it was already the case in the 2011 PPS study.

In Belgium as well as in a majority of EU countries MRSA percentages are steadily and significantly decreasing (**Figure 14**). In 2019, the EARS-BE monitoring recorder its lowest ever prevalence (6.3% MRSA; n= 1,276), and a faster decrease than European averages. This decrease is likely the consequence of the efficient implementation of national recommendations and guidance documents on preventing the spread of MRSA.

Next to MRSA, vancomycin-resistant *S. aureus* (VRSA) is classified by the WHO as a high priority antibiotic resistant organism. In Belgium, resistance to vancomycin among invasive *S. aureus* clinical isolates is anecdotal.

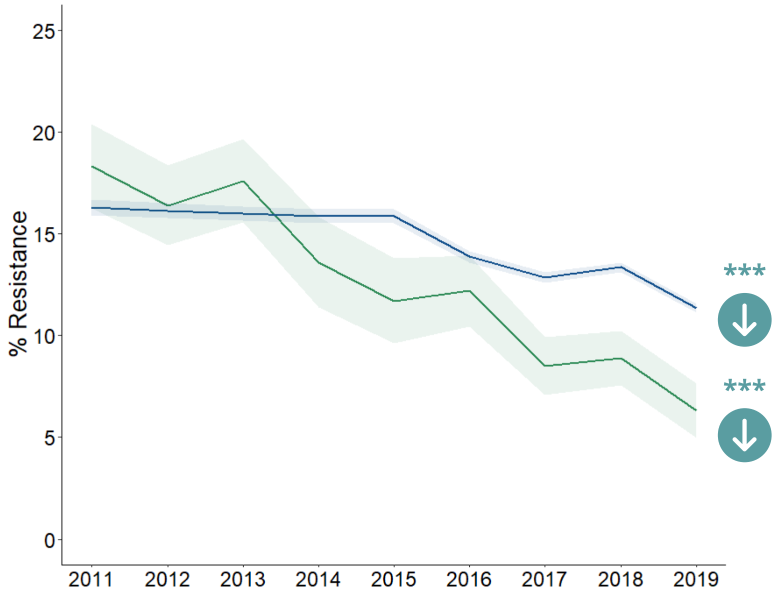

Figure 14. Proportion of invasive clinical isolates of MRSA isolated in Belgium (green) in comparison to EU averages labeled in blue. Source: EARS-BE data and ECDC's Surveillance Atlas of Infectious Diseases.

5.2.6 *Enterococcus faecium*

Enterococci are part of the normal intestinal flora of humans and animals. However, when this commensal relationship is disrupted, they can cause a large variety of invasive diseases such as urinary tract infections, bloodstream infections and endocarditis. The genus Enterococcus includes more than 17 species, but the vast majority of clinical enterococcal infections in humans are caused by *E. faecalis* and *E. faecium*. The 2017 PPS study estimated that 4.8% of HAI were caused by E. faecalis, making it the 4th most often isolated pathogen from HAI in Belgium. *E. faecium* was less commonly isolated and reported to cause 1.2% of HAI in Belgium[14].

Enterococci are intrinsically resistant to a broad range of antimicrobial agents including cephalosporins, sulphonamides and low concentrations of aminoglycosides. Due to the expression of low affinity penicillin-binding proteins, they exhibit decreased susceptibility to many beta-lactam agents. However, there is commonly *in vitro* synergy between cell-wall active agents (penicillins or glycopeptides) and aminoglycosides. Some enterococci have developed high resistance to aminoglycosides, causing loss of any synergy with this class of antibiotic[44]. Vancomycin-resistant *E. faecium* (VRE) belongs to the high priority antibiotic resistant organisms list of the WHO.

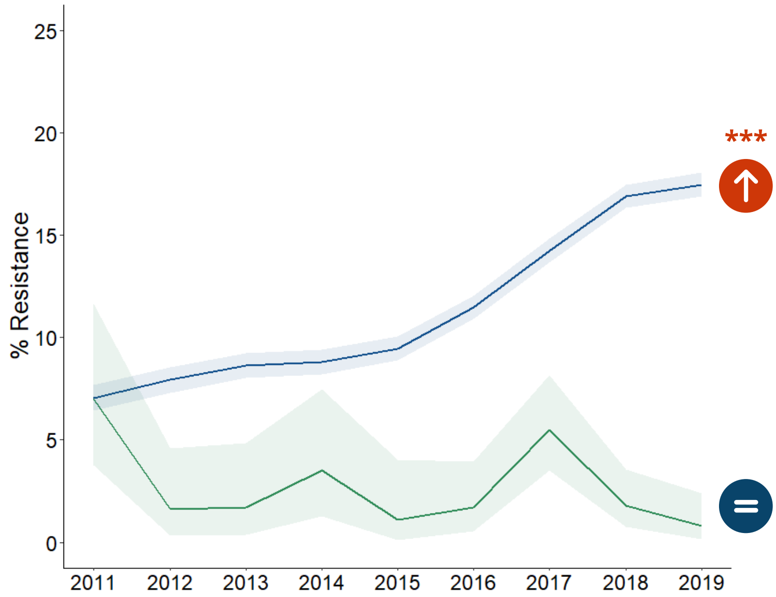

Figure 15. Proportion of invasive clinical isolates of vancomycin-resistant E. faecium isolated in Belgium (green) in comparison to EU averages labeled in blue. Source: EARS-BE data; 2011–2019

As shown in **Figure 15** above, in Belgium, the vancomycin resistance among *E. faecium* invasive clinical isolates remained low during the last decade. The highest resistance rate detected in 2017 (5.5%) might be indicative of outbreaks in some hospitals as shown from the percentiles of the distribution of lab means[45]. When comparing the medians for 2017 and other years, which are less sensitive to extreme values than the mean, these are all equal to 0.0%. Notably, Belgium goes against the EU-wide trend, with clearly increasing prevalence and 17.5% VRE isolates (2847/16295) reported in 2019.

5.2.7 *Streptococcus pneumoniae*

Streptococcus pneumonia is a gram-positive bacterium that often resides as a commensal in the human respiratory tract, with the highest carriage prevalence occurring in children (<5 years). Nevertheless, asymptomatic carriage can also evolve to respiratory infections such as otitis media and pneumonia or even invasive pneumococcal disease (IPD) like bacteremia and meningitis. About 100 pneumococcal serotypes have been defined based on the capsular type. After the introduction of pneumococcal conjugate vaccines (PCVs), the global annual number of severe cases in children dropped from 14.5 million to 9.2 million in 2015. Belgium initiated a universal pediatric immunization PCV program, installing the 7-valent PCV in 2007 followed by switches to 13-valent PCV (PCV13) in 2011 and to 10-valent PCV in 2015-2016, while reinstalling PCV13 in 2019. Annually, over 1500 isolates are being send to the NRC in the context of epidemiological surveillance of IPD.

Specific pneumococcal serotypes are associated with antimicrobial resistance. The introduction of the PCVs resulted in a decreased circulation of some penicillin resistant serotypes, resulting in a decrease of penicillin resistance overall shortly after the introduction of PCV7 (2007). During the period of 2011 to 2019, penicillin resistance remained stable over time (mean of 10% of resistant strains).

This stable trend and the level of resistance are in accordance with European data. In 2020, an increase in penicillin resistance is observed (**Figure 16**), mainly resulting from a change in antimicrobial susceptibility method. Furthermore, the number of IPD cases in 2020 was heavily impacted by the COVID-19 crisis, making it more difficult to compare resistance rates of 2020 to the rates of the previous years. For macrolides, a mean prevalence resistance rate of 19% has been observed over the years, with a decline since 2014 and a stable resistance rate of about 15% for the period 2015-2019.

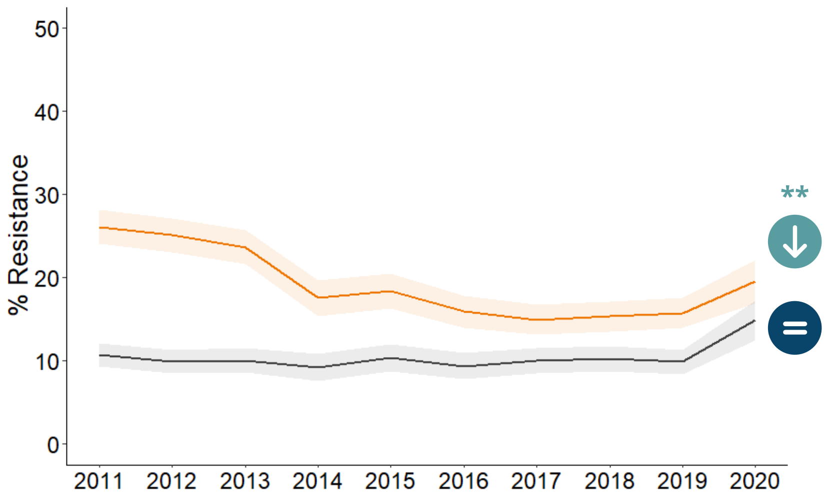

Figure 16. Evolution of penicillin (grey) and macrolide (orange) resistance in invasive *S. pneumoniae* isolates send to the NRC, between 2011 and 2020. For this report strains with penicillin MIC above 0.06mg (=epidemiological cut-off) were categorized as penicillin resistant. Data source: NRC Invasive *S. Pneumoniae.*

5.2.8 *Haemophilus influenzae*

H. influenzae is a Gram-negative coccobacillus part of the normal upper respiratory tract flora. The presence or absence of a polysaccharide capsule allows the classification of H. influenzae strains into typeable (serotypes a to f) and non typeable (NTHi) strains. The colonization of the upper respiratory tract begins early in infancy and is a dynamic process. At least 75% of healthy adults are colonized with *H. influenzae*, usually NTHi. As observed for *S. pneumoniae*, the nasopharynx acts as a potential reservoir for infection and asymptomatic carriage of *H. influenzae* can lead to both respiratory tract and systemic infections, including meningitis and bacteremia. In the early nineties, the introduction of a H. influenzae serotype b (Hib) conjugate vaccine in Belgium led to a sharp decrease in Hib invasive infections (from very common to rare) and most invasive infections now occur in older patients with concurrent conditions. Annually, about one hundred invasive isolates are referred to the NRC by over forty clinical laboratories. NTHi strains are responsible for more than 75% of invasive diseases and particularly affect children under five and adults over sixty-five. Among encapsulated strains, serotype f, frequently encountered among patients over 65 years of age, is dominant.

Ampicillin resistance in *H. influenzae* is mediated by two separate mechanisms: beta-lactamase production (most frequently) or amino-acid substitution of the transpeptidase enzyme (PBP3) encoded by the *ftsI* gene. Between 2011 and 2020, ampicillin resistance rate among invasive *H. influenzae* strains isolated in Belgium fluctuated around twenty percent. On average, less than 20% of the resistant strains did not produce beta-lactamase and were classified as phenotypic “beta-lactamase negative-ampicillin resistant” *H. influenzae*. In 2019, an increase in the proportion of amoxicillin-clavulanic acid association resistant strains (11%) is noticed that is not confirmed in 2020. However, the COVID-19 crisis in 2020 makes any interpretation difficult and particular vigilance is required in the coming years.

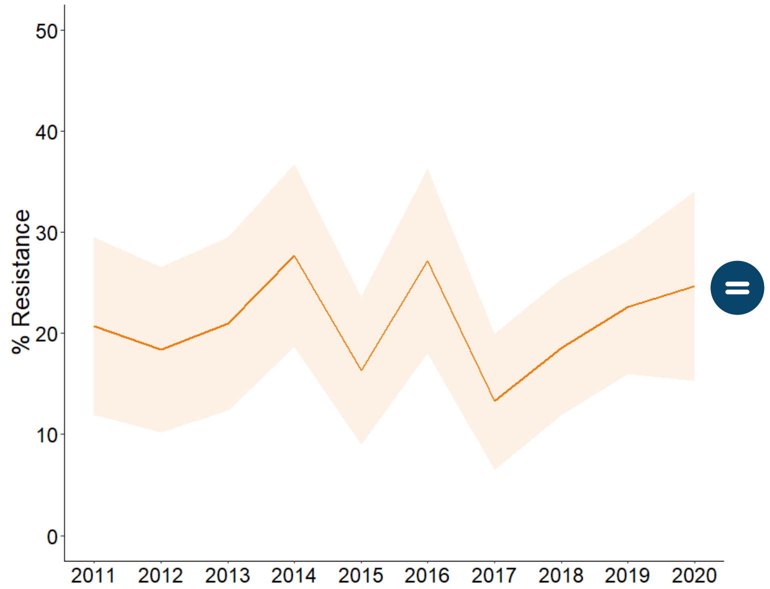

Figure 17. Evolution of resistance to ampicillin in invasive H. influenzae isolates send to the NRC for typing, 2011-2020.

5.2.9 *Typhoid Salmonella spp.*

Salmonella serovar *Typhi* and the various pathovars of *S. Paratyphi* are commonly referred to as typhoidal *Salmonella* serovars, and are restricted to human host. When ingested in contaminated food or water, they penetrate the small bowel epithelium, enter the lymphoid tissue and spreads by lymphatic and hematogenous routes to cause typhoid fever. In contrast to non-invasive *Salmonella* infections (Section 4), prophylactic treatment is required.

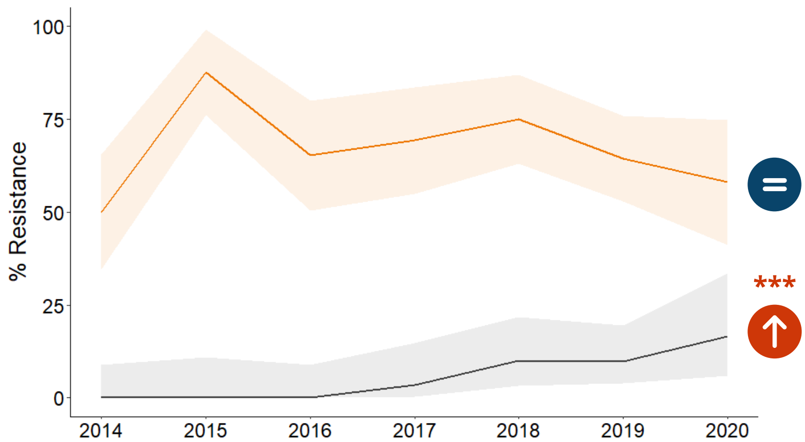

Figure 18. Evolution of resistance to ciprofloxacin (orange) and 3[rd] generation cephalosporins (grey) in Typhoid *Salmonella spp.* send to the NRC for typing, 2014-2020.

Typhoidal serovars are uncommon in Belgium, typically associated with travel and represent on average 1.5% of the approx. 3,000 submitted isolates at the NRC. While resistance in *S. Paratyphi* A and B isolates (approx. 15/y) remains uncommon, the majority of S. Typhi (approx. 30/y) isolates are resistant to fluoroquinolone (**Figure 18**). Worryingly, significantly increasing levels 3GC resistance are being noted, reaching 16.5% in 2020. Less than 5% of Belgian typhoid *Salmonella* strains are resistant to macrolides.

5.3 LUNG INFECTIONS

5.3.1 *Mycobacterium tuberculosis*

Tuberculosis (TB) is caused by infection with the bacterium *Mycobacterium tuberculosis* (Mtb) and predominantly affects the lungs, resulting in extensive tissue pathology. Of high global concern are relapse infections of multidrug resistant (MDR-TB) strains, 8.5% of which globally are extensively drug resistant (XDR-TB). This XDR-TB is a rare type of MDR-TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one linezolid or bedaquiline. In Belgium, annual registers of infections with *M. tuberculosis* (TB) are published by the Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding (VRGT) and Fonds des Affections Respiratoires (FARES), based on the mandatory reporting of cases[46]. These publications show a stagnation of the annual cases of TB around 9/100,000 inhabitants.

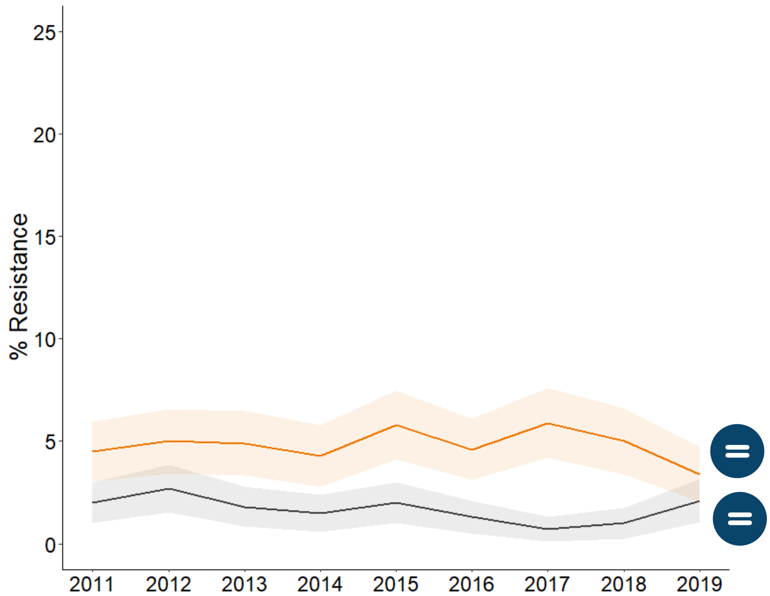

Figure 19. Overview of AMR in Belgian *M. tuberculosis* isolates, indicating the percentage of strains monoresistant against isoniazid (orange) and MDR strains (grey). Data source: TB registers 2011-2019.

The majority of Belgian TB isolates remain pan-susceptible to antibiotics. On average 4.8% of the isolates are monoresistant to isoniazid and 1.7% and MDR-TB. In the considered period (2011-2019), the proportion of drug-resistant strains remained stable (**Figure 19**). The occurrence of XDR-TB remains extremely rare in Belgium (<0.5%).

5.4 SEXUAL TRANSMISSIBLE INFECTIONS

5.4.1 *Neisseria gonorrhoeae*

Neisseria gonorrhoeae is the causative agent of Gonorrhea, the second most frequently found sexually transmitted infection (STI) in Belgium. Gonorrhea is predominantly found among men between 20-39 years of age. The number of cases found by molecular detection is increasing over time.

To be able to follow up antimicrobial susceptibility to ciprofloxacin, ceftriaxone and azithromycin, Sciensano recommends to ship identified gonococcal isolates to the national reference center for STIs for further antibiotic susceptibility testing[47]. On average, 600 N. gonorrhoeae isolates are tested annually.

Although ciprofloxacin resistance remains stable around 50%, a sharp increase in azithromycin resistance is noted over the last five years (2015: 0.8% to 16.0% in 2020) (**Figure 20**). The proportion of β-lactamase producing *N. gonorrhoeae* strains has been stable around 15%, while resistance due to chromosomal mutations in penicillin binding proteins declined significantly from 27% in 2014 to 4.9% in 2020. Currently, the use of dual therapy of azithromycin/ceftriaxone (first-line treatment in many European countries) to treat *N. gonorrhoeae* is being discussed as almost no resistance to ceftriaxone is observed (0.4% in 2020). Quinolones/fluoroquinolones are not recommended as first-line treatment.

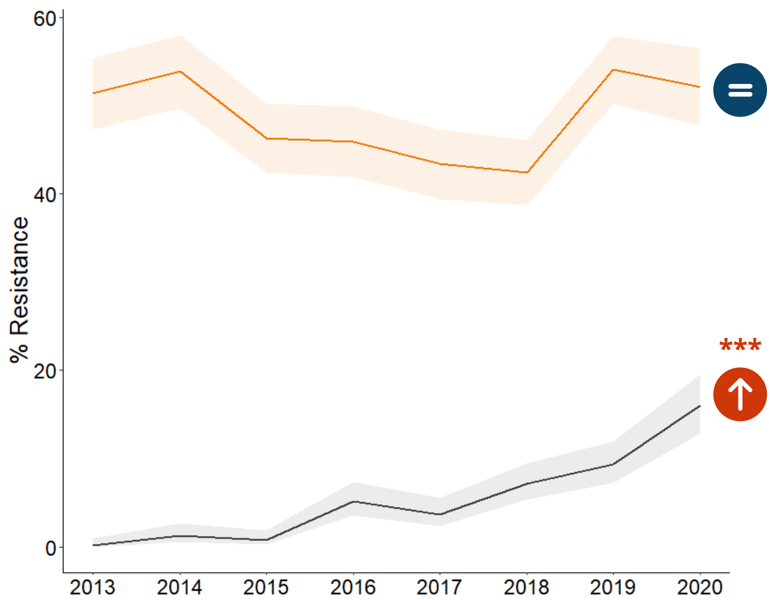

Figure 20. Evolution of ciprofloxacin (orange) and macrolide (grey) resistance in *N. gonorrhoeae* isolates sent to the NRC for typing, between 2011 and 2020.

5.4.2 *Mycoplasma genitalum*

Mycoplasma genitalium causes non-gonococcal non-chlamydial urethritis/cervicitis but is also frequently found in asymptomatic individuals. This micro-organism is gaining more importance due to the rapid speed it is acquiring resistance to the first- and second-line treatment (ie. azithromycin and moxifloxacin). At the NRC, which analyses 40-50 isolates per year, resistance to azithromycin and moxifloxacin is estimated by detecting resistance-associated mutations (RAMs) in 23S rRNA gene and *par*C at position 83/87.

As seen in **Figure 21**, the number of cases resistant for macrolides is almost reaching 80% and approximately one out of three samples harbors RAMs to both microbials. Resistance figures are much higher in men (and especially among men who have sex with men) compared to women (macrolides: 33% vs 91%; Macrolides/FQL: 22% vs 33%). In addition, most of the samples received in 2020 were of male origin (79%). As such, these figures should be interpreted cautiously.

Due to the asymptomatic nature and the increasing numbers of resistance to the first- and second- line treatment, it is currently not recommended anymore to screen for this microorganism or to treat asymptomatic infections.

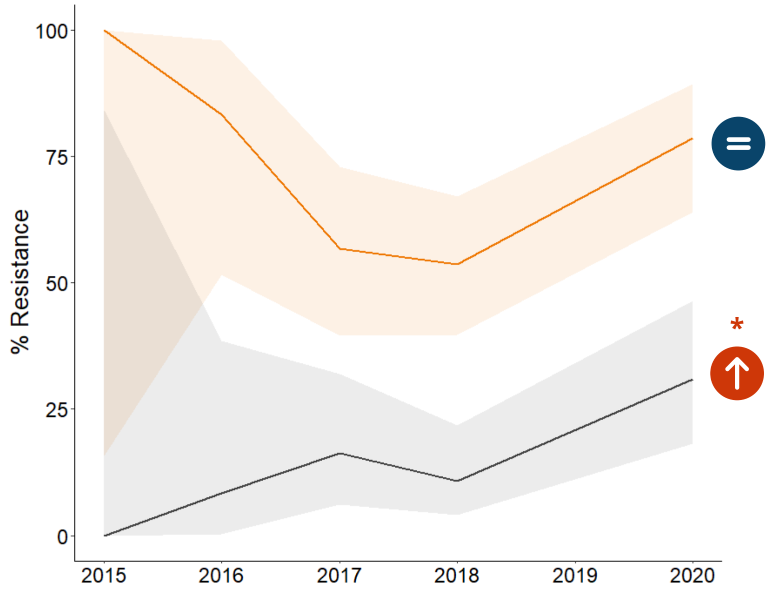

Figure 21. Evolution of macrolide (orange) and macrolide + fluoroquinolone (grey) resistance in *M. genitalium* isolates sent to the NRC for typing, between 2015 and 2020.

5.5 GASTROINTESTINAL INFECTIONS

5.5.1 *Helicobacter pylori*

Helicobacter pylori is a Gram-negative bacterium that colonizes the antrum and corpus of the stomach. It is known to induce chronic inflammation of the underlying mucosa (chronic active gastritis) and can cause major upper gastrointestinal diseases: gastric and duodenal peptic ulcers, gastric cancer and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma. The prevalence of *H. pylori* infections varies according to geographical regions, as well as between different ethnic, social or age groups, and can reach to 50% in developing countries. In a study in 2011, a sample of Belgian asymptomatic children and young adults were tested for *H. pylori* with an overall prevalence recorded at 11% with a strong relation to country origin abroad[48].

The Maastricht IV/Florence Consensus report for management of *H. pylori* infection[49] advised that recommended treatment strategies should be based on the regional prevalence of antimicrobial resistance (15% resistance rate considered as the threshold) that directly influenced the choice and efficacy of drug regimens.

The NRC of *H. pylori* reported stable primary resistance (no exposure to previous *H. pylori* eradication treatment) rates to clarithromycin around 20% (**Figure 22**) among *H. pylori* (more than 700 isolates per year) detected in samples collected from limited number of hospital-based endoscopic units mainly from the Brussels and Wallonia region.

In 2018, a prospective multicentric multinational European study investigated the proportion of primary antibiotic resistance cases of *H. pylori* and correlated to the data collected in 2008–2017 on the antibiotic consumption in the community from 18 European countries[50]. The mean *H. pylori* CLA-R rate was 21.4% overall (17.4% in Belgium) and was significantly higher in Central/Western/Southern than in the Northern European countries ($p<0.03$). A significant association was found between *H. pylori* CLA-R and consumption in the community of macrolides ($p=0.0003$). Based on current resistance rates to clarithromycin and to levofloxacin that remained high (both above 15%) despite stabilization over the past decade, *H. pylori* treatment regimens including these two antibiotics should not be started without susceptibility testing in most European countries including Belgium.

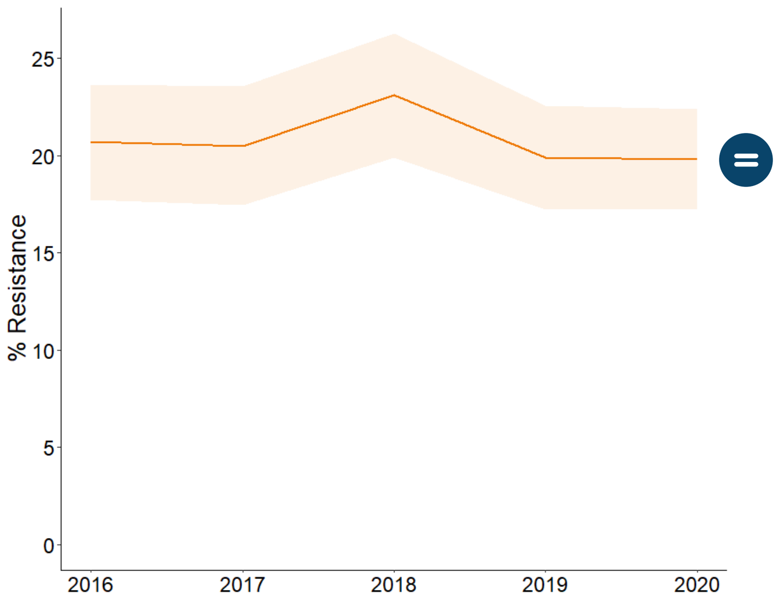

Figure 22. Evolution of clarithromycin resistance in *H. pylori* isolates send to the NRC for typing, between 2016 and 2020.

5.5.2 Shigella species

Shigella are Gram-negative pathogenic Enterobacterales which cause severe dysentery with diarrhea, fever, and stomach cramps. Humans are the main reservoir of Shigella, and transmission occurs mainly through contaminated food or water via the fecal-oral route. In Belgium, *S. sonnei* is the most frequently reported species representing 75% of the approx. 400 annually received isolates at the NRC, while *S. flexneri* accounts for approx. 20% of cases. Of note, the reported number of Shigella infections imploded with 70% during the COVID pandemic, most likely due to travel restrictions and social distancing measures.

International travel to high endemic regions as well as sexual transmission via oral–anal contact, especially in MSM, contributes to infection. As shown in a study of the NRC in 2021[51], more and more ciprofloxacin and macrolide-resistant *S. sonnei* lineages are internationally circulating among the MSM population. Since 2017, one third of *S. sonnei* strains encode resistance to first-line antibiotics: 7% to Ciprofloxacin, 6% to Azithromycin and 23% to both. In *S. flexneri*, the resistance to ciprofloxacin and azithromycin is on the rise as well. Of additional worry is the simultaneous increasing the prevalence of plasmid-encoded ESBL genes in the last five years (**Figure 23**).

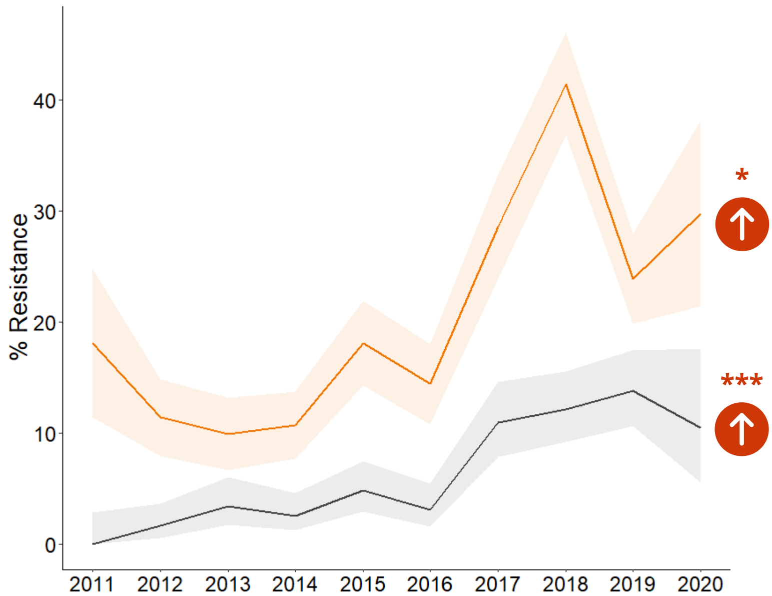

Figure 23. Overview of resistance to ciprofloxacin (orange) and 3rd generation cephalosporins (grey) among Shigella spp. in Belgium, as recorded by the NRC between 2011 and 2020. The observed peak in ciprofloxacin resistance in 2018 was related to a large outbreak of MDR *S. sonnei* in the MSM community. Data source: NRC Shigella.

5.6 FUNGAL INFECTIONS

5.6.1 *Candida spp.*

Over 200 Candida species have been identified, with both *C. albicans* and *C. glabrata* being ubiquitous commensals of the human skin, oral cavity and gastrointestinal tract. However, they are also the two most common pathogenic yeasts. Under certain predisposing factors, they can cause superficial and invasive infections, associated to high morbidity and mortality, being responsible for >60% of all systemic candidiasis. Candidaemia is estimated to cause over 500 cases and 200 deaths annually in Belgium. In 2020, respectively 34% and 30% of the isolates that were sent to the NRC for susceptibility testing, were identified to be *C. albicans* and *C. glabrata*.

While *C. albicans* is considered to be susceptible to all antifungals and resistance is rarely reported, *C. glabrata* has often found to be associated to decreased susceptibility to fluconazole, and most worrying an emerging resistance to echinocandins.

Based on data of the NRC between 2011 and 2020, antifungal resistance of *C. albicans* to fluconazole remains stable over time, ranging between 0.7% and 4.4% (**Figure 24a**), much lower than what is internationally reported (7-12%). Antifungal resistance is more concerning for *C. glabrata*, for which a mean proportion of 16.7% of the strains were confirmed to be resistant to fluconazole in Belgium, however characterized by large fluctuations in prevalence over time, largely due to the low sample sizes (**Figure 24b**). Internationally, levels of resistance up to 36% have been reported, remaining fairly constant over the last years. Echinocandins, the preferred treatment for *C. glabrata*, on the contrary, are currently faced with an emerging resistance. Data of the NRC show a mean prevalence of resistance to anidulafungin of 1.9%, with an upper limit of 5%.

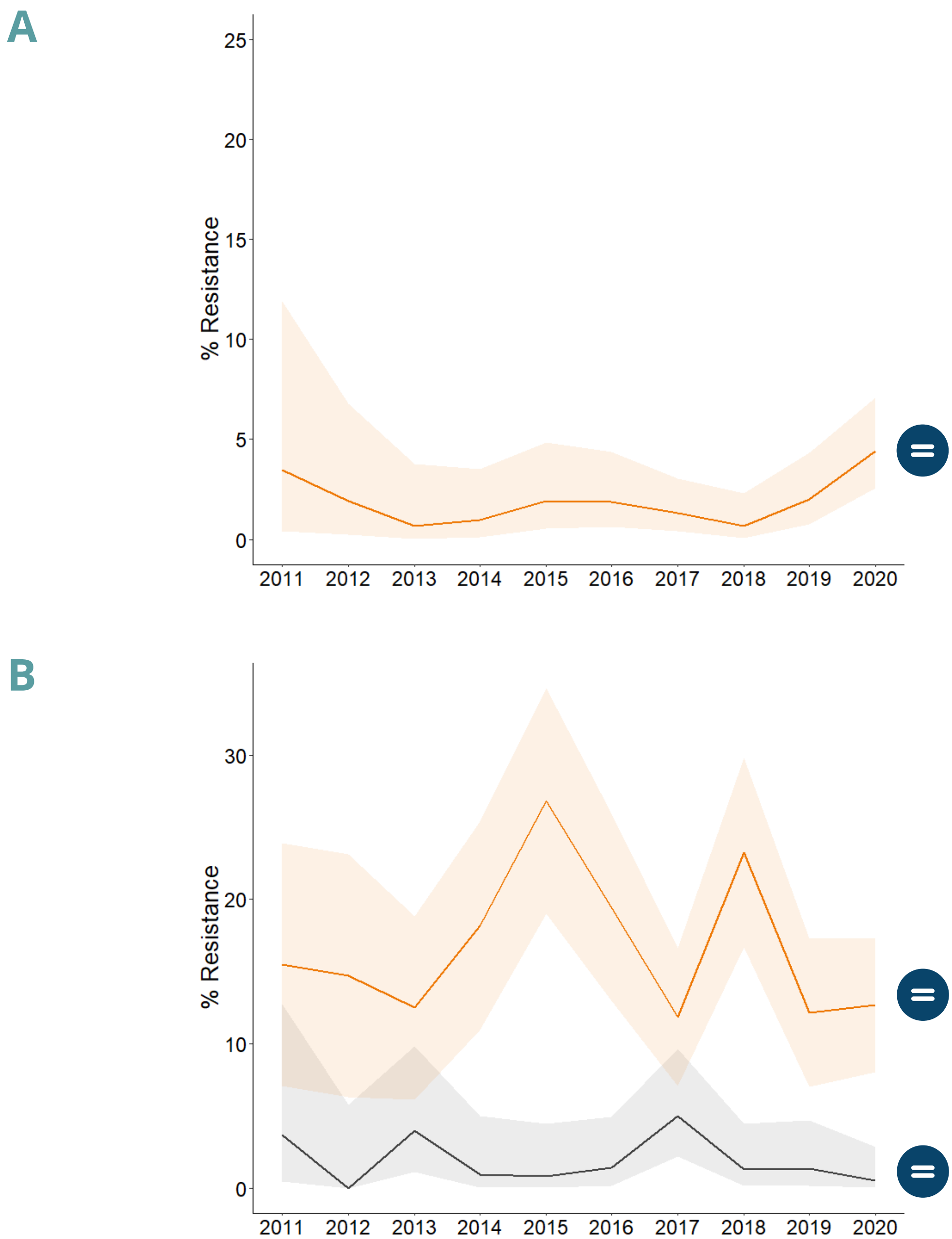

Figure 24. Overview of resistance to fluconazole (orange) and the echinocandin anidulafungin (grey) among *Candida albicans* (A) and *Candida glabrata* (B) in Belgium, as recorded by the NRC between 2011 and 2020.

5.6.2 *Aspergillus fumigatus*

Aspergillus fumigatus is an environment globally distributed mold that can cause a variety of diseases that differ in severity and clinical presentation, affecting patients with asthma to immunocompromised patients. In the latter patient population, aspergillosis remains an important cause of morbidity and mortality, worldwide causing >200,000 infections annually. Risk factors for invasive fungal infections have evolved over time, most recently associated to the viral infection COVID-19, especially for *A. fumigatus* in ICU patients. In 2020, about 10% of the fungal isolates that were sent to the NRC for susceptibility testing, were identified to be *A. fumigatus* species (complex).

Resistance to triazole antifungals (posaconazole, voriconazole, isavuconazole and itraconazole) in *A. fumigatus* is emerging and is becoming a worldwide concern. A person can develop a triazole-resistant infection after prolonged antifungal therapy or by inhalation of resistant spores. The most commonly reported associated resistance mechanisms in *A. fumigatus* are mutations in the cyp51A gene. Since 2016, all *A. fumigatus* complex isolates are screened for triazole-resistance at the NRC. A stable trend was observed (**Figure 25**), with an overall triazole-resistance prevalence of 7.1%. The majority of these resistant isolates displayed resistance to all triazole antifungals tested[52]. The reported prevalence of triazole-resistance worldwide in *A. fumigatus* varies between 0.6% and 36.3%. Since the last multicenter cohort study on *Aspergillus* resistance among patients with *Aspergillus* disease in Belgium was conducted in 2011-2012[53], a new national surveillance effort is scheduled for the year 2022. Isolates from patients with disease will be collected in hospitals across the entire country and susceptibility testing will be performed at the NRC.

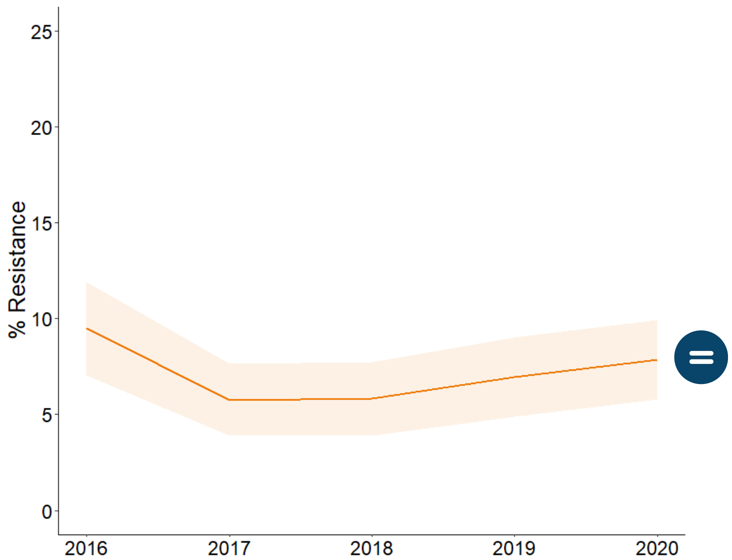

Figure 25. Overview of resistance to the azole class among *Aspergillus fumigatus* species complex in Belgium, as recorded by the NRC between 2016 and 2020. Prior 2016, no systematic screening of triazole-resistance was in place.

6 ZOONOTIC PATHOGENS IN HUMAN AND FOOD

A zoonosis is an infectious disease that has jumped from an animal to humans. Zoonotic pathogens may be bacterial, viral or parasitic that can spread to humans through direct contact or through food, water or the environment. Many of these micro-organisms are commonly found in the intestines of healthy food-producing animals. The most common zoonotic diseases are caused by consuming food or drinking water contaminated by pathogenic bacteria, such as *Salmonella spp*. and *Campylobacter spp*.

Antimicrobial resistance can be a complicating factor in the control of a severe zoonotic infection. The use of antibiotics increases the potential for drug-resistant strains of zoonotic pathogens capable of spreading quickly in animal and human populations. Today, most MDR *Salmonella spp*. strains found in food producing animals in Belgium did not arise from the local use of antibiotics but were introduced through trade.

6.1 METHODOLOGY

Data on AMR in human salmonellosis was collected from the NRC Salmonella, which receives annually approx. 3,000 samples and is the only laboratory in Belgium performing routine serotyping of S. enterica. A 2021 study concluded that the coverage of the NRC surveillance system was estimated to be 83-85%, allowed reliable estimates of resistance levels based on NRC data[54]. In contrast, AMR data could not be based on data from the NRC Campylobacter, as there is a bias towards submission of resistant isolates (Dr. Delphine Martiny, personal communication). Instead, we collected ciprofloxacin and erythromycin resistance data from routine analysis of *C. jejuni* isolated from stool specimens (2011-2020, n=3,970) in two large hospitals, i.e. LHUB-ULB and CHU Liège.

For non-human samples, the European Directive 2003/99/EC provides that Member States ensure a monitoring that provides comparable data on the occurrence of antimicrobial resistance in zoonotic agents and, in so far as they present a threat to public health, other agents. This monitoring should supplement the monitoring of human isolates conducted in accordance with Decision No 1082/2013/EU. European Decision 2013/652/EU further harmonizes the data collection at EU-level between 2014 and 2020. In odd years in Belgium, *Salmonella spp*. isolates are collected from animal feed as well as in poultry (broilers and fattening turkeys) before slaughter (faeces), at slaughter (skin neck), and in fresh meat from broilers. In even years, Salmonella spp. isolates are collected from the food hygiene criterion monitoring at slaughterhouse level (pigs and veal calves) and in fresh meat from pigs and bovines. The number of Salmonella isolates to be included in the antimicrobial resistance monitoring is 170 for each study population.

Antimicrobial surveillance of *C. jejuni* includes sampling in the caecal content of broilers and turkeys at slaughter as described by the European Decision 2013/652/UE. A minimum of 170 Isolated *C. jejuni* from caecal samples at the slaughter house are tested for resistance to ciprofloxacin, nalidixic acid, tetracyclin, erythromycin, streptomycin, gentamycin according to the method described by the European Decision 2013/652 / EU.

In food samples, C. jejuni was isolated from broilers carcasses and poultry meat according to ISO 10272-1. Broiler samples were pre-enriched in Bolton broth, whereas direct spread of caecal sample from poultry onto selective agar was performed.

6.2 *SALMONELLA SPP.*

Non-typhoidal *Salmonella* (NTS) serovars are considered as the second main cause of food-borne outbreaks. They can have an extensive host range, and humans infections by these organisms generally result in self-limiting disease. As resistance patterns of *Salmonella* are strongly serovar-specific, we present data from three most prevalent serotypes from human isolates, veterinary and food sources, covering >70% of all *Salmonella* samples in all sectors (**Table 2**).

Table 2. Overview of the most prevalent Salmonella serotypes identified across sectors in Belgium, 2014-2020.

Human sector			Chickens			Pork/Bovine		
Serotype	N_{total}[a]	$\%_{total}$[a]	Serotype	N_{total}[b]	$\%_{total}$[b]	Serotype	N_{total}[b]	$\%_{total}$[b]
Typhimurium	10,051	59.5	Infantis	205	38.0	Typhimurium	185	46.8
Enteritidis	3,311	19.6	Paratyphi B var, L(+) Tartrate+	108	20.0	Derby	105	26.6
Infantis	397	2.4	Enteritidis	76	14.1	Rissen	14	3.5

[a] Analysed at the NRC Salmonella between 01/01/2014 and 31/12/2020.
All isolates are from human patients.

[b] Analysed at the NRL AMR between 01/01/2014 and 31/12/2020.
All isolates are from animal carcases.

In the 2014-2020 period, resistance in non-typhoid *Salmonella* serovars remains generally low across sectors, with 12% among human *Salmonella* isolates reported to be MDR in 2020 (all serotypes combined). Ciprofloxacin resistance (MIC_{CIP}>0.06 µg/ml) recently increased in human Typhimurium, Enteritidis and Infantis isolates (**Figure 26**). However, high levels of ciprofloxacin resistance (MIC_{CIP}>2 µg/ml) remain rare, and mainly confined to isolates from serovar Kentucky which represents only 1% of human infections. In non-human samples, highest levels of ciprofloxacin resistance are observed in *S. Infantis* isolates from chickens.

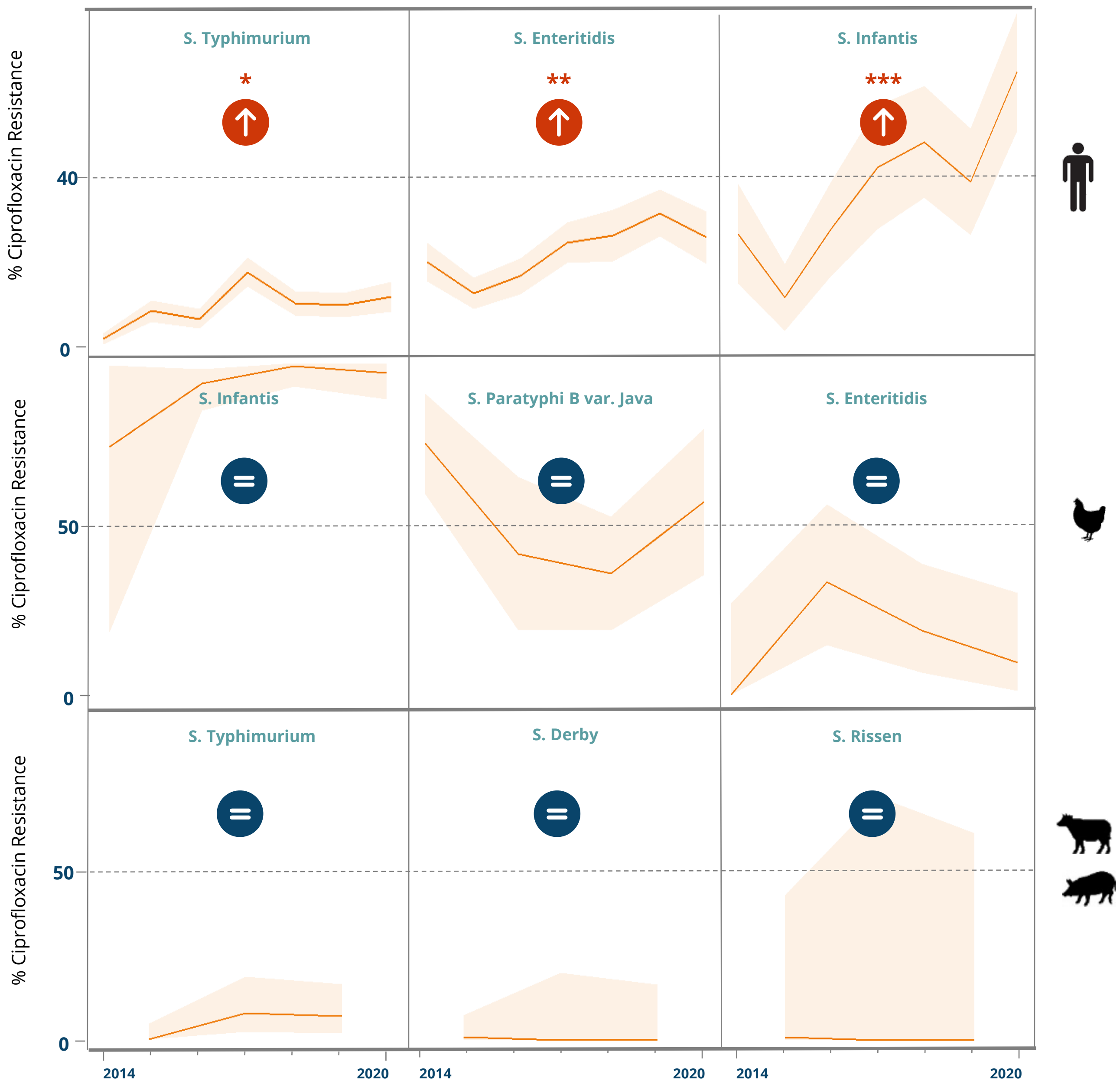

Figure 26. Overview of ciprofloxacin resistance in the main Salmonella serovars isolated from humans, chickens and bovine/pork. In all isolates, the breakpoint of 0.064 µg/ml is used to define ciprofloxacin resistance. Data source: NRC Salmonella and NRL, 2014-2020.

Regarding β-lactam resistance, ampicillin resistance is high in serovars Typhimurium across sectors. The occurrence of extended spectrum β-lactamases is <5% for all serotypes and sectors, apart from a peak of 9.1% in human serovars Infantis isolates in 2018. The resistance against macrolides (MIC_{AZM}>16 µg/ml) remained below 5% in the last five years across sectors and serovars.

The highest proportion of multidrug resistance in human Salmonella samples is found in serovar Infantis (41% in 2020). Apart from ciprofloxacin resistance due to GyrA mutations, this can be linked to the international spread of the pESI megaplasmid, carrying multiple AMR genes, in S. Infantis from human and[55]. In Salmonella samples from pork and bovine, resistance to critical antibiotics is rare (<5%).

6.3 CAMPYLOBACTER JEJUNI

Although Campylobacteriosis is not often treated with antimicrobials, some severe infections need to be treated and macrolides are first-line antibiotics, while fluoroquinolones, tetracyclines and aminoglycosides remain as alternative drugs. Poultry are a major source of *Campylobacter*, and in particular *C. jejuni*, the species most frequently associated with digestive campylobacteriosis in humans.

Among human *C. jejuni* isolates, we observed a very high percentage of resistance to ciprofloxacin, with an increasing trend since 2011. Very similar, stable resistance levels are recorded in poultry meat and veterinary isolates with >50% resistant isolates (**Figure 27**). Almost half of the isolates of poultry meat also show a combined pattern of resistance including ciprofloxacin, nalidixic acid and tetracycline. In contrast, resistance levels for erythromycin remain below 1% in samples from both human and non-human sector.

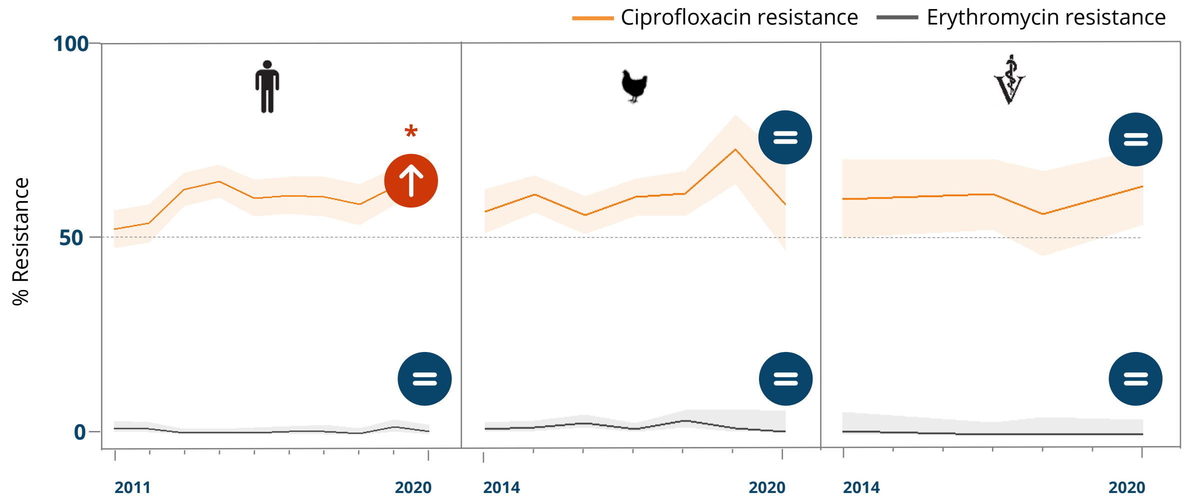

Figure 27. A. Overview of resistance to the ciprofloxacin and erythromycin among *C. jejuni* isolated from (i) routine stool specimens in LHUB-ULB and CHU Liège (2011-2020, n=3,970), (ii) poultry meat and (iii) veterinary samples. Source of datasets (ii) and (iii): ref. 43.

7 AMR IN FOOD-PRODUCING ANIMALS

BELMAP uses AMR data from commensal *E. coli* isolated from healthy animals as a general indicator for resistance among food-producing animals. *E. coli* is an indicator bacterium that can be frequently isolated from all animal species. Its resistance levels reflect the magnitude of the pressure exerted by antibiotics in the population, and can be used as an indicator of emergence and change. Besides *E. coli*, MRSA is monitored in different animal categories to map both the prevalence of this resistant zoonotic bacterium and its level of resistance to other antibiotics.

7.1 METHODOLOGY

For commensal *E. coli* monitoring, samples of fresh faeces are collected annually since 2011 by the Federal Agency for the Safety of the Food Chain (FASFC) as part of a nationwide surveillance program. The following categories of food-producing animals are included: veal calves, beef cattle (meat production), broiler chickens and fattening pigs. The sampling and isolation of indicator E. coli strains are performed according to standardized technical instructions, details of which are available in the reports of FASFC[56].

Indicator bacteria are tested on susceptibility to ciprofloxacin, cefotaxime, colistin and 11 other antibiotics, as determined by European legislation (2013/652/EU). Since 2014, all the isolates showing resistance to a third generation cephalosporin and considered as suspected β-lactamase producing *E. coli*, and are analyzed in detail for their β-lactamase activity. Besides the monitoring of commensal E. coli, European Decision 2013/652/EU also harmonizes the selective monitoring of β-lactamase, AmpC and carbapenemases producing *E. coli* isolated from caecal samples gathered at slaughter from broilers, fattening turkeys, fattening pigs and veal calves and from fresh meat samples from broilers, pigs and bovines. Outside the EU- context, a monitoring of *E. Coli* ESBL in fish and raw milk is monitored in Belgium.

The surveillance of MRSA follows a 3-year cycle and includes farm samples (pool of nasal swabs) from poultry, cattle, or pig categories, depending on the year. The detection of MRSA isolates is based on a pre-enrichment followed by a selective enrichment with cefoxitin (3.5 mg/l) and aztreonam (75 mg/l), followed by plating on chromogenic agar (Brillance MRSA2 agar, Oxoid). Presence of MRSA is suspected based on colony morphology and confirmed using a triplex real-time PCR method detecting the *S. aureus* specific gene, nuc, the presence of the *mec*A gene responsible for methicillin resistance and the variant *mec*C gene. AMR testing of MRSA strains is detailed in the reports available on the FASFC website. The confirmed MRSA isolates are spa-typed by sequencing the repetitive region of the *spa* gene encoding for the staphylococcal protein A (www.ridom.de/staphtype), and categorized as livestock associated (LA) MRSA if they are associated to the *S. aureus* clonal complex CC398 through PCR[57].

7.2 ESCHERICHIA COLI

In the BELMAP report, we report on commensal *E. coli* isolated from four different animal species: veal calves, young beef cattle, broiler chickens and pigs. Results for fully sensitive *E. coli* are presented in green in **Figure 28**. Large differences exist between the animal groups. The highest proportion of fully sensitive *E. coli* strains are isolated from beef cattle, with a significant increase in susceptible strains and a record level of 78% pan-susceptible strains in 2020. Likewise, the proportion of multidrug resistant (MDR) *E. coli* declined significantly between 2011 and 2020. In the three other monitored food producing animal populations (broiler chickens, pigs and veal calves), no significant changes in the proportion of fully susceptible and MDR *E. coli* strains are observed (2011-2020). The levels of MDR *E. coli* are highest in poultry.

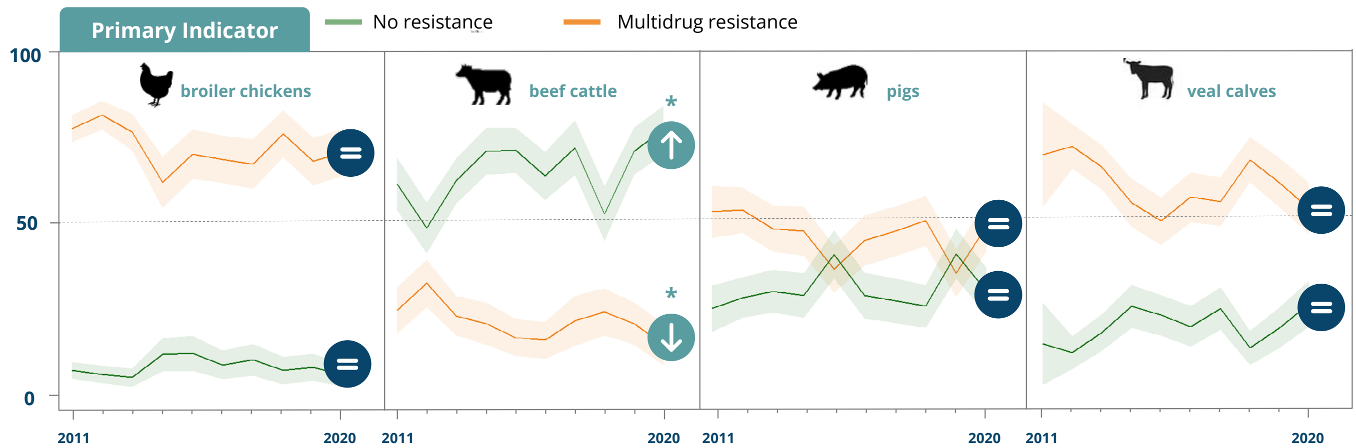

Figure 28. Proportion of fully sensitive *E. coli* (green) and multidrug resistant (red) strains isolated from chickens, beef cattle, pigs and veal calves, from 2011 to 2020. Data source: FASFC reports[50].

Regarding the individual resistances against critical antibiotics, encouraging results are also observed. In poultry, beef cattle and veal calves, we observe a significant decrease in ciprofloxacin resistance (MIC>0.06 µg/ml) considering the entire 2011-2020 period, reaching its lowest levels ever recorded in 2020 (**Figure 29**). Likewise, the occurrence of colistin resistance in veal calves declined significantly and is <3% since 2014. For all other of these species, the prevalence of the ciprofloxacin, colistin and cephalosporin resistance remained stable and very low, i.e. below 10% over the years.

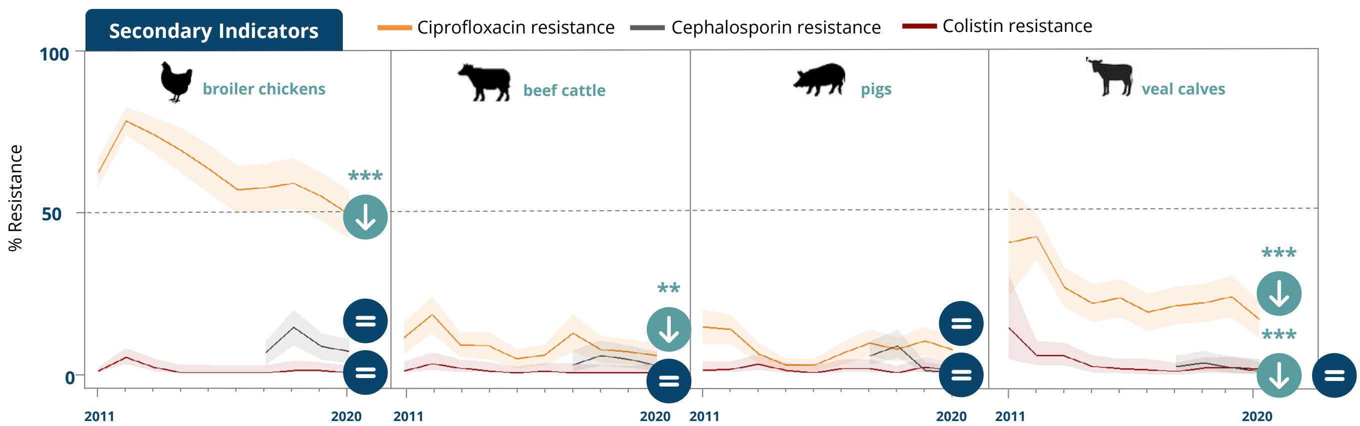

Figure 29. Prevalence of non-susceptibility to ciprofloxacin (orange), cephalosporins (grey) and colistin (red) in commensal E. coli isolated strains isolated from chickens, beef cattle, pigs and veal calves, from 2011 to 2020. Data source: FASFC reports[50].

7.3 MRSA

The prevalence of MRSA was monitored since 2011 based on a 3-year rotation for each animal category in the following order: poultry, cattle and pigs (three to four data points). Analysis of the odd ratios points at a significant decline MRSA prevalence in pigs between 2013 and 2019. The prevalence remained very high (between 50 and 70%) in pigs for the 3 data points, and in veal calves in 2018 (while variable among the 3 data points). In bovines for meat and dairy cows, the prevalence was low to moderate. In poultry (broilers and layers), the prevalence was low.

In all monitored animal categories, most of the MRSA isolates were genotyped as livestock associated (LA) MRSA. The detailed genotypes and their relative occurrence can be found in the different yearly reports available on the FASFC website. During the last years of the MRSA monitoring in cattle (2018), pigs (2019) and poultry (2020), the prevalence of LA-MRSA was 93.1% (94/101), 100% (170/170) and 100% (4/4), respectively. Hospital acquired (HA) or community acquired (CA) MRSA genotypes have also been found in animal samples (pigs, cattle or poultry) sporadically over the past years. The source was not traced. In the future, the whole genome sequencing analysis of such HA/CA-MRSA strains from animal origin together with strains from human origin would allow to compare these strains to assess more in depth their genetic relatedness.

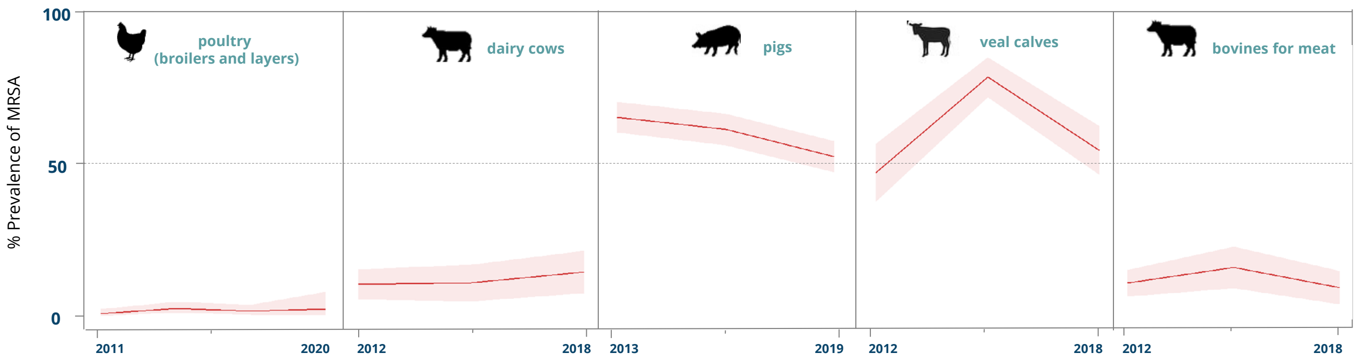

Figure 30. Prevalence of MRSA in poultry (broilers and layers), dairy cows, pigs, veal calves and bovines for meat observed since 2011 based on a 3-year rotation monitoring. Given only three datapoint, no statistical analysis was performed. Data source: FASFC reports[50].

8 ANTIBIOTIC RESIDUES AND RESISTANCE IN THE ENVIRONMENT

8.1 RESIDUE MONITORING

The environment is increasingly acknowledged as a contributor to the development and spread of AMR, in particular in high risk areas due to human, animal and manufacturing waste streams. All Belgian regions adhere to the European Directive 2008/105/CE on environmental quality standards in the field of water policy. The Vlaamse Milieumaatschappij (VMM), Brussels Environment and the Société Wallonne des Eaux (SWDE) track the concentration of potential water pollutants of surface water listed in the European Watch List. The most recent version of this list contains five antibiotics: three macrolides (erythromycin, clarithromycin, azithromycin), ciprofloxacin and amoxicillin[58]. The report also defines Predicted No Effect Concentrations (PNECs)[59] and identifies possible methods of analysis for the proposed substances.

In none of the surveilled surface waters, azithromycin and ciprofloxacin were detected during the 2016-2020 monitoring campaigns. Of note, the PNEC of azithromycin (0.019 µg/L) resembles closely the detection limit of current technology (0.02 µg/L). Amoxicillin was detected once, but its concentration (0.054 µg/L) did not exceed the PNEC of 0.089 µg/L. Clarithromycin was retrieved in approx. 50% of all samples, but its PNEC (0.12 µg/L) was exceeded only once (Sambre in Namur, 2018, 0.13 µg/L). Finally, erythromycin was detected in the Sambre in Namur in five consecutive measurements since 2018 at an average concentration of 0.012 µg/L, well below the PNEC (0.04 µg/L)[60].

Apart from these mandatory monitoring, an encouraging number of point prevalence studies have been initiated by the regional authorities.

- The IMHOTEP project (2018) investigated drug residues in 208 water samples from effluents from purification stations, surface and drinking water in Wallonia[61].
- The Interreg project DIADEM (2017-2020) mapped yearly fluctuations in residue concentration of 7 antibiotics in 24 sites spread alongside Meuse, Sambre and the Semois.
- The VMM published various reports on residues in surface and ground water[62,63,64]
- ILVO (Instituut voor Landbouw en Visserij Onderzoek) is also very active in this reseach area. For example, they published recently on residues in cattle farmyard manure[65], pig slurry[66], and the removal of antibiotic residues and zoonotic bacteria during biological nitrogen removal from swine manure over time[67].

8.2 RESISTANCE MONITORING

The monitoring of AMR in environmental samples, typically through investigation of resistance profiles of *E. coli* isolated from various environmental sources, is not systemically organized in Belgium. Some point prevalence studies have been undertaken recently, the most ambitious being the Antibiobug project (Institut Scientifique de Service Public) in 2019.

In two sampling campaigns, the presence of antibiotic-resistant bacteria in surface waters in Wallonia was evaluated. In total 938 *E. coli* strains were sampled from 24 locations alongside main Walloon rivers. In total 30% of these *E. coli* samples were resistant to amoxicillin, and 15% were MDR. Importantly, *E. coli* from hospital effluent displayed resistance to meropenem (0.4%) and ertapenem (1.5%). A follow-up study (Antibiobug 2) is ongoing , focusing on bathing water. A new project started in 2020, called EBLSE, whose aim is to study extended spectrum beta-lactamase producing *E. coli* by phenotypic, genotypic (CTX-M genes) and whole genome sequencing tests in freshwaters, hospital effluents and wastewater treatment plants.

The role played by disinfectants should not be neglected. These biocidal products are used in particular for disinfecting hands or disinfecting surfaces and more importantly since the health crisis linked to the coronavirus. This is why the de Duve Institute carried out a literature review, at the instigation of the FPS Public Health, to assess the role played by the use of these biocides in the emergence of antimicrobial resistance[68]. This report summarizes the scientific research carried out to date on the role of biocides of product types 1 (human hygiene) and 2 (disinfectants and algaecide products not intended for direct application to humans or animals). In some cases, resistance to a biocidal agent also confers resistance to an antibiotic or other biocidal agent, a phenomenon referred to as cross resistance. The report also focuses on the main active substances of disinfectants authorized in the European Union. The authors found that there is indeed a role for biocides in the development of antimicrobial resistance. The most problematic active substances are chlorhexidine, quaternary ammonium compounds and triclosan. Resistance to these disinfectant active substances may also confer cross resistance to certain antibiotics such as tetracycline, vancomycin, chloramphenicol, ciprofloxacin, imipenem and colistin.

9 RECOMMENDATIONS

The BELMAP editorial board supports the actions outlined in the NAP-AMR to strengthen antimicrobial stewardship in humans and animals, and to improve infection control and prevention in acute care hospitals and long-term care facilities. On top of these efforts, we would like to lay attention on the following points of possible improvement for the surveillance of antimicrobial use and resistance.

Two important blind spots in current monitoring of AMR lie in the **community sector** and the **environment**. For the human community sector, a structural surveillance should be established at the first-line health care through the participation of private laboratories. A first step might be the inclusion of representatives of these general practitioners serving laboratories in the technical committee on MDROs. For the monitoring of resistance in the environment, structural funding should be provided to build on existing knowledge generated by point prevalence studies like Antibiobug (Chapter 8). Moreover, a structural funding for AMR in clinical isolates is missing and should be provided, at very least for resistance in invasive isolates as requested by ECDC.

We also suggest further harmonization of data collections to avoid duplicate registration and to allow streamlining of efforts. In the animal sector, data collections for resistance among animal pathogens, are currently provided by DGZ and ARSIA, but also private veterinary laboratories should be encouraged to report or publish their AMR data of pathogens. Members of these organizations will also be invited to join the BELMAP editorial board. Harmonization and sharing of databases will improve the understanding of transmission chains within and between the different sectors of human, animal and environmental health in a One-Health approach.

Evidence of resistance following the use of biocidal products begins to be gathered and more importantly this resistance may confer cross resistance to antibiotics. It seems therefore important to consider resistance to problematic disinfectant active substances (i.e. chlorhexidine and quaternary ammonium compounds) in national monitoring programs as well. The role of the disinfectants in the emergence of AMR deserves more attention from the health care sector.

For surveillance of antimicrobial consumption in human medicine, follow-up **stratified by indication** (or diagnostic group – not limited to infectious diseases) in a quantitative way through time would improve the benchmarking with similar hospitals, and would allow to select appropriate actions to improve the compliance with BAPCOC guidelines. Secondly, extending the hospital surveillance to long term care facilities, in particular **nursing homes**, would also be of major interest for this frail population. Thirdly, further analyses of sales data and/or hospital data are needed to give a view on **non-reimbursed consumption** of antibiotics (e.g. fluoroquinolones in the community, cefedirocol and daptomycin in hospitals) with special focus on recently released large-spectrum antimicrobials (e.g. ceftazidime/avibactam), which is currently missed in the surveillances based on reimbursement data.

Another important area of improvement is the ability to detect relevant **resistances and their molecular mechanism**, not only at the NRC but also at the local level. This might need financial incentives to perform specialized rapid diagnostic tests through reimbursement by National Insurance. This could be coupled to nomenclature with possible restriction to the newly acknowledged profession of medical microbiologist, which is also part of the NAP-AMR.

The implementation of these testing methods in routine labs is of particular importance for the specific surveillance of carbapenemase producers (CP) among Gram-negative rods (Enterobacterales, *P. aeruginosa*, *A. baumannii*) that need to be distinguished from non-CP carbapenem-resistant (CR) strains. The appropriate detection/distinction of CP and the study of the distribution of the different carbapenemase families has major clinical impact both for the individual therapeutic management (especially in invasive infections) and for the prevention and control of resistance transmission in a healthcare setting.

Besides this improved capacity, we propose to elaborate a **national platform for rapid reporting** of alert cases related to HA-AMR/MDRO and their follow-up/management by designated actors.

Key in such a platform is the broad roll-out of **Whole-Genome Sequencing**, at least for all MDRO isolates with high dissemination potential (e.g. carbapenemase-producing organisms), zoonotic pathogens and emerging pathogens in both human and animal sectors. This is absolutely required to track the major circulating MDR strains in Belgium, and the presence of high-risk clones. Belgium lags far behind to most European countries in the implementation of this technology, hampering international cluster detection and outbreak investigation. Investment in WGS will allow, in short term, a dynamic monitoring both at the macro-epidemiological surveillance level of circulating clones in human and animal populations, and at the micro-epidemiological level for an optimized management of local outbreaks. This task, with specific funding, should be in part attributed to NRCs and NRLs (in collaboration with Sciensano) because they hold the knowledge and expertise in their respective field of competence.

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2. Premixes are veterinary medicinal product intended for incorporation into animal feedingstuffs, i.e. feed where antimicrobials are mixed in the before or at delivery on farm.

3. For the community sector, broad spectrum antibiotics include only penicillins, cephalosporins, macrolides and fluoroquinolones.

4. Categoric hospitals offer specialized, isolated or chronic care, i.e. treating a condition which is not acute.

5. Les prémélanges sont des médicaments vétérinaires destinés à être incorporés dans les aliments pour animaux, c'est-à-dire des aliments pour lesquels des antimicrobiens sont mélangés avant ou au moment de la livraison à la ferme.

6. Pour le secteur ambulatoire, les antibiotiques à large spectre comprennent uniquement les pénicillines, les céphalosporines, les macrolides et les fluoroquinolones.

7. Premixen zijn veterinaire medicinale producten, die bedoelt zijn om gemengd te worden met dierenvoeding, voor of na de levering in de boerderijen.

8. In de ambulante sector zijn breed-spectrum antibiotic beperkt tot penicillines, cephalosporines, macrolides en fluoroquinolones.

9. Categorische ziekenhuizen beiden gespecialiseerde, geïsoleerde of chronische zorg aan.

10. Für den Gemeinschaftssektor umfassen Breitbandantibiotika nur Penicilline, Cephalosporine, Makrolide und Fluorchinolone.

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