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Impact of changes in the WHO's 2019 update of DDDs on the measurement of adult hospital antibacterial consumption in Catalonia (Spain), 2008–18

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Objectives: In 2019 the WHO fully adopted new DDD values. The objective of this study is to analyse their impact on the measurement of consumption of antibacterials in hospitals participating in the Catalan Infection Control and Antimicrobial Stewardship National Program (VINCat-PROA) in Catalonia (Spain) between 2008 and 2018.

Methods: The anatomical therapeutic chemical/DDD system was used to monitor adult hospital antibacterial consumption expressed in DDD/100 bed-days. Consumption from 2008 to 2018 was calculated using both pre- and post-update DDD values. Differences were calculated as the percentage variation in DDD/100 bed-days and analysed with Student's *t*-test. Simple linear regressions were performed to evaluate the trends in adult antimicrobial consumption over the study period.

Results: The overall consumption according to post-update DDD values decreased by 12.2% ($P < 0.001$) compared with the pre-update DDD values. Penicillins (−19.6%; $P < 0.001$) and carbapenems (−19.0%; $P = 0.023$) showed the greatest reduction, followed by cephalosporins (−7.7%; $P = 0.021$) and quinolone antibacterials (−7.7%; $P = 0.017$). ICU services showed the greatest overall reduction (−13.1%; $P < 0.001$). From 2008 to 2018 there was a statistically significant decrease in consumption of penicillins and quinolone antibacterials and a statistically significant increase in cephalosporin and carbapenem consumption with both pre- and post-update DDD values. There were no variations in the ranking of consumption between the pre- and post-update DDD values.

Conclusions: The WHO's updates of DDDs have had a significant impact on the measurement of antibacterial consumption. In our region, they have corrected an overestimation of penicillin and carbapenem consumption amounting to 19%. It is essential to bear these findings in mind for an accurate assessment of temporal trends and benchmarking.

Introduction

WHO[1] and ECDC[2] agree that the analysis of the consumption of antibacterials is crucial in order to optimize their use and to bring down resistance rates. A relationship between the use of certain antimicrobials and increased resistance has been proposed.[3]

The anatomical therapeutic chemical/DDD (ATC/DDD) system, developed and updated by the WHO Collaborating Centre for Drug Statistics Methodology, has become an international standard for drug metrics and facilitates the presentation and comparison of drug consumption statistics at international, national and regional levels.[4] In 2008 the Catalan Infection Control and Antimicrobial

Stewardship National Program (VINCat-PROA) adopted the ATC/DDD system as a standardized measure.

In 2018, the WHO International Working Group for Drug Statistics Methodology updated the DDD of eight commonly used antibiotics as a result of a review of the doses used in clinical practice. These new DDD values were fully adopted in 2019.[5]

The objective of this study is to analyse the impact of these changes on the measurement of the consumption of hospital antibacterials for systemic use by adults in Catalonia (Spain) between 2008 and 2018.

Materials and methods

During the study period the number of hospitals participating in VINCat-PROA rose from 46 in 2008 to 63 in 2018. These figures represented 68.8% and 85.7% of all adult acute hospital beds in Catalonia (a region of 7.6 million people), respectively. The number of bed-days recorded increased from 2 991 053 in 2008 to 3 714 938 in 2018.

The ATC/DDD system was used to monitor adult hospital antibacterial consumption.[6] The pharmacy departments at the participating hospitals reported the number of units of each antibacterial for systemic use (J01) dispensed and bed-days data from the whole hospital and from the medical and surgical services and ICUs. Annual antibacterial consumption, expressed in DDD/100 bed-days, was calculated using both pre-update DDD values (WHO ATC/DDD index 2017) and post-update DDD values (WHO ATC/DDD index 2019), keeping the number of units used and bed-days of every single year.

The percentage difference in mean consumption between pre- and post-update DDD values was calculated and the significance of differences between values was established by Student's *t*-test. Simple linear regressions were performed to evaluate the trends in consumption over the study period. The linear relationship was checked by ANOVA tests, and Pearson's correlation coefficients (Pc values) were obtained. Values of $P < 0.05$ were considered statistically significant. A two-tailed distribution was assumed for all *P* values.

Results

Impact of DDD update on the mean consumption of antibacterials for systemic use

During 2008–18 the overall mean adult hospital antibacterial consumption calculated with post-update DDD values decreased by 12.2% ($P < 0.001$) compared with the pre-update DDD values: 79.4 versus 69.7 DDD/100 bed-days (Table 1). Penicillins showed the greatest reduction [−19.6% ($P < 0.001$), 31.7 versus 25.5 DDD/100 bed-days], followed by carbapenems [−19.0% ($P = 0.023$), 5.4 versus 4.4 DDD/100 bed-days], cephalosporins [−7.7% ($P = 0.021$), 13.8 versus 12.7 DDD/100 bed-days] and quinolone antibacterials [−7.7% ($P = 0.017$), 12.3 versus 11.3 DDD/100 bed-days].

Mean consumption decrease in all services and ICUs showed the greatest overall reduction (−13.1%, $P < 0.001$). In ICUs, carbapenems were the most affected by the update (−25.1%, $P < 0.001$). Penicillins had the greatest reduction in both medical (−20.9%, $P < 0.001$) and surgical services (−18.4%, $P < 0.001$).

Ampicillin and colistin had the largest reductions in consumption (−66.4%, $P < 0.001$ and −59.6%, $P < 0.001$, respectively); however, amoxicillin/β-lactamase inhibitors showed the greatest impact in terms of overall reduction in consumption, due to its extended use (25.3% and 23.0% of the total antibacterial consumption with pre- and post-update DDD values, respectively). Antibiotics of special interest such as meropenem (−31.6%, $P = 0.03$) and cefepime (−50.1%, $P < 0.001$) also presented notable reductions in consumption.

Impact of DDD update on the evolution of consumption of antibacterials for systemic use

From 2008 to 2018 (Figure 1, annual overall consumption data on demand) there was a decrease in consumption of penicillins with both pre-update DDD values (33.5 versus 29.4 DDD/100 bed-days, Pc = −0.92, $P < 0.001$) and post-update DDD values (26.10 versus 24.24 DDD/100 bed-days, Pc = −0.72, $P = 0.012$). Differences between pre- and post-update values showed a reduction from −22.2% in 2008 to −17.5% in 2018, mainly due to a decrease in amoxicillin/β-lactamase inhibitor consumption (23.6 versus 17.3 DDD/100 bed-days with pre-update DDD values, and 17.8 versus 14.2 DDD/100 bed-days with post-update DDD values).

Consumption of quinolone antibacterials showed a statistically significant reduction with both pre-update (12.4 versus 10.4 DDD/100 bed-days, Pc= −0.76, $P < 0.001$) and post-update values (11.6 versus 9.6 DDD/100 bed-days, Pc = −0.78, $P = 0.004$). Differences increased from −5.9% in 2008 to −7.5% in 2018.

Cephalosporin consumption increased from 2008 to 2018 with both pre-update (12.0 versus 14.7 DDD/100 bed-days, Pc = 0.94, $P < 0.001$) and post-update DDD values (10.9 versus 13.9 DDD/100 bed-days, Pc = 0.95, $P < 0.001$). Differences fell from −9.5% in 2008 to −5.5% in 2018, mainly due to an increase in cefazoline (1.9 versus 3.3 DDD/100 bed-days) and ceftriaxone (3.8 versus 5.5 DDD/100 bed-days) consumption and the maintenance of cefepime consumption both pre-update (1.6 versus 1.6 DDD/100 bed-days) and post-update (0.7 versus 0.7 DDD/100 bed-days).

Consumption of carbapenems increased from 2008 to 2018 with both pre-update (3.4 versus 6.9 DDD/100 bed-days, Pc = 0.99, $P < 0.001$) and post-update DDD values (3.4 versus 5.4 DDD/100 bed-days, Pc = 0.99, $P < 0.001$). Differences rose from −3.5% in 2008 to −22.3% in 2018, due to a reduction in imipenem consumption (1.8 versus 0.9 DDD/100 bed-days) combined with an increase in meropenem consumption with both pre-update (1.2 versus 4.6 DDD/100 bed-days) and post-update DDD values (1.1 versus 3.1 DDD/100 bed-days).

Impact of DDD update on relative consumption of antibacterials for systemic use

There were no variations in the ranking of consumption between the pre- and post-update DDD values regarding the total consumption of all antibiotic groups during the study period. Penicillins were the most used and represented 35.0% and 32.2% of the total adult hospital antibacterial consumption with both pre- and post-update DDD values, followed by cephalosporins (17.5% and 18.4%, respectively) and quinolone antibacterials (12.4% and 12.8%, respectively). The group 'other antibacterials' (J01X) occupied the fourth place (11.7% and 12.5%, respectively) followed by carbapenems, which represented 8.3% and 7.2% of all antibacterial consumption, respectively.

Table 1. Mean antibacterial consumption pre- and post-update of the WHO DDDs according to drugs and hospital service (Catalonia 2008–18)

Service	ATC classification	Pre-update values, DDD/100 bed-days, mean (SD)	Post-update values, DDD/100 bed-days, mean (SD)	Percentage decrease	*P*
Total	J01 Antibacterials for systemic use	79.44 (2.13)	69.75 (2.51)	12.2	<0.001
	J01C Penicillins	31.66 (1.67)	25.46 (0.83)	19.6	<0.001
	J01CA01 Ampicillin	2.38 (0.24)	0.80 (0.08)	66.4	<0.001
	J01CA04 Amoxicillin	1.59 (0.27)	1.06 (0.16)	33.6	<0.001
	J01CR02 Amoxicillin/β-lactamase inhibitor	20.14 (2.24)	16.06 (1.22)	20.3	<0.001
	J01DBCDE Cephalosporins	13.80 (0.90)	12.73 (1.09)	7.7	0.021
	J01DE01 Cefepime	1.76 (0.14)	0.88 (0.09)	50.1	<0.001
	J01DH Carbapenems	5.40 (1.18)	4.37 (0.73)	19.0	0.023
	J01DH02 Meropenem	3.15 (1.19)	2.15 (0.71)	31.6	0.030
	J01M Quinolone antibacterials	12.29 (0.91)	11.34 (0.79)	7.7	0.017
	J01MA02 Ciprofloxacin	5.80 (0.59)	4.91 (0.52)	15.3	0.001
	J01XB01 Colistin	0.75 (0.12)	0.31 (0.10)	59.6	<0.001
ICU	J01 Antibacterials for systemic use	143.65 (4.32)	124.78 (3.70)	13.1	<0.001
	J01C Penicillins	42.89 (3.62)	37.47 (2.81)	12.6	0.001
	J01CA01 Ampicillin	4.79 (0.43)	1.59 (0.12)	66.9	<0.001
	J01CA04 Amoxicillin	1.11 (0.46)	0.71 (0.27)	36.1	<0.001
	J01CR02 Amoxicillin/β-lactamase inhibitor	17.10 (2.70)	15.45 (1.81)	9.7	0.022
	J01DBCDE Cephalosporins	22.71 (1.21)	19.72 (0.85)	13.1	<0.001
	J01DE01 Cefepime	5.54 (1.14)	2.66 (0.47)	50.2	<0.001
	J01DH Carbapenems	20.49 (2.64)	15.35 (1.16)	25.1	<0.001
	J01DH02 Meropenem	15.38 (4.21)	10.36 (2.41)	32.7	<0.001
	J01M Quinolone antibacterials	13.94 (1.24)	12.03 (1.24)	13.6	0.002
	J01MA02 Ciprofloxacin	6.93 (0.91)	4.82 (0.71)	30.5	<0.001
	J01XB01 Colistin	5.32 (1.01)	1.99 (0.52)	62.6	<0.001
Medical	J01 Antibacterials for systemic use	78.99 (2.79)	69.14 (1.94)	12.5	<0.001
	J01C Penicillins	33.04 (2.23)	26.12 (1.32)	20.9	<0.001
	J01CA01 Ampicillin	2.36 (0.31)	0.81 (0.08)	65.8	<0.001
	J01CA04 Amoxicillin	1.87 (0.34)	1.24 (0.20)	33.6	<0.001
	J01CR02 Amoxicillin/β-lactamase inhibitor	21.86 (2.63)	17.01 (1.54)	22.2	<0.001
	J01DBCDE Cephalosporins	13.80 (0.90)	12.73 (1.09)	10.3	0.002
	J01DE01 Cefepime	2.44 (0.21)	1.19 (0.11)	51.2	<0.001
	J01DH Carbapenems	4.78 (1.19)	4.00 (0.73)	16.4	0.078
	J01DH02 Meropenem	2.63 (1.01)	1.86 (0.54)	29.2	<0.001
	J01M Quinolone antibacterials	14.61 (1.20)	13.98 (1.02)	4.3	0.197
	J01MA02 Ciprofloxacin	4.57 (0.46)	3.93 (0.41)	13.7	0.003
	J01XB01 Colistin	0.70 (0.14)	0.29 (0.12)	58.4	<0.001
Surgical	J01 Antibacterials for systemic use	74.76 (3.86)	66.55 (4.38)	11.0	<0.001
	J01C Penicillins	29.78 (1.19)	24.38 (0.82)	18.4	<0.001
	J01CA01 Ampicillin	2.31 (0.23)	0.78 (0.09)	66.4	<0.001
	J01CA04 Amoxicillin	1.48 (0.29)	0.97 (0.15)	34.8	<0.001
	J01CR02 Amoxicillin/β-lactamase inhibitor	18.68 (1.64)	15.27 (0.82)	18.2	<0.001
	J01DBCDE Cephalosporins	14.34 (1.50)	13.81 (1.63)	3.7	0.443
	J01DE01 Cefepime	0.69 (0.16)	0.34 (0.08)	51.3	<0.001
	J01DH Carbapenems	4.63 (0.99)	3.78 (0.64)	18.3	0.027
	J01DH02 Meropenem	2.48 (0.97)	1.66 (0.61)	32.9	<0.001
	J01M Quinolone antibacterials	9.39 (0.69)	8.36 (0.71)	10.9	0.003
	J01MA02 Ciprofloxacin	7.12 (0.69)	6.09 (0.66)	14.5	0.002
	J01XB01 Colistin	0.37 (0.12)	0.15 (0.07)	60.0	<0.001

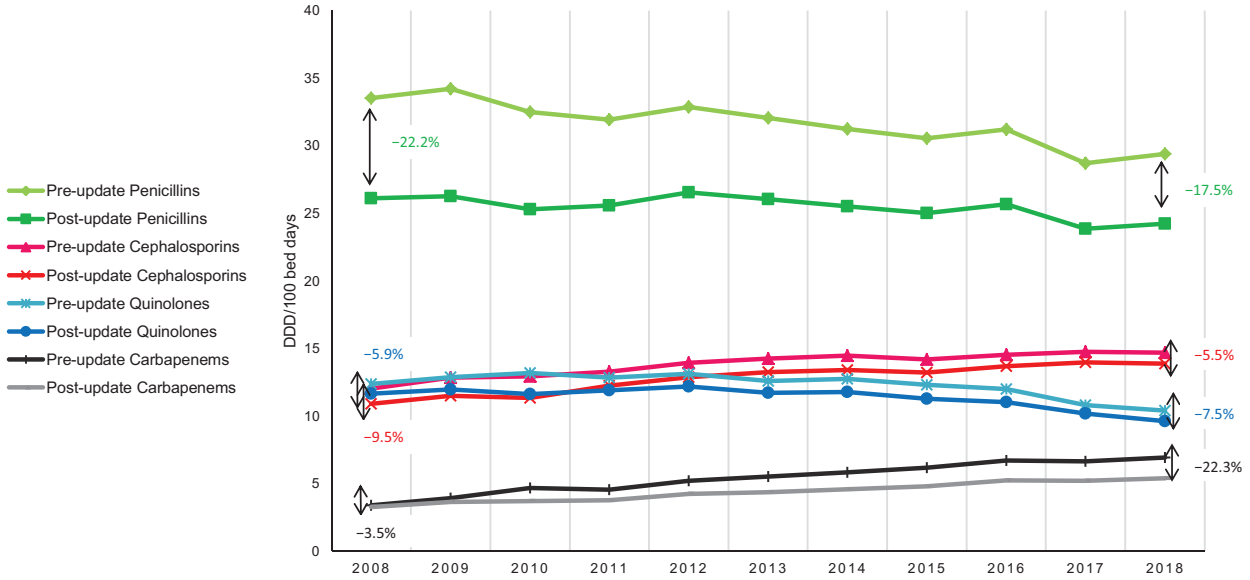

Figure 1. Evolution of consumption of antibacterials for systemic use (J01) pre- and post-update of the WHO DDDs (Catalonia 2008–18). Percentages show differences in consumption values between pre- and post-update in 2008 and 2018.

Discussion

The reduction in the measurement of adult hospital antibacterial consumption in our study (12.2%) is similar to that reported by Robertson *et al.*,[7] who estimated a total DDD per 1000 inhabitants-day reduction on average by 12.0%, and confirms that the WHO's 2019 DDD update corrects an overestimation of the consumption of antibacterials for systemic use (especially in penicillins) that had already been detected by Haug and Reikvam[8] in Norway, Charra *et al.*[9] in France and the EU, and Klein *et al.*[10] in their study of antibiotic consumption in 76 countries. Carbapenems (meropenem) were more affected by DDD changes in ICU services since patients are more complex and the use of broad-spectrum antibiotics is higher.

This reduction in the measurement related to the update of DDD values did not affect the main trends in the evolution of antibacterial consumption observed during our study period. Similar reductions in penicillin use were observed by Dickstein *et al.*[11] in Israel and an increase in the consumption of first- and third-generation cephalosporins was observed by Kwint *et al.*[12] in the Netherlands and Grau *et al.*[13] in Catalonia. The reduction in quinolone consumption from 2008 to 2018 observed with both pre- and post-update DDD values could be related to the association of fluoroquinolones with an increased risk of aortic aneurysm and dissection.[14] Meropenem is the only carbapenem affected by the DDD update and the upward trend in its consumption, together with the downward trend in the consumption of imipenem due to adverse effects associated with its use,[15] can explain the great increase in the difference between the pre- and post-update consumption in 2008 (−3.5%) and 2018 (−22.3%). Despite the increase in the use of carbapenems, in the last few years their consumption has stabilized throughout Europe.[16]

The changes in DDD values have not included other groups of antibiotics such as tetracyclines (J01A), sulphonamides and trimethoprim (J01E), macrolides, lincosamides and streptogramins (J01F), aminoglycoside antibacterials (J01G) or other antibacterials (J01X); however, the general ranking of relative consumption has not been affected. Penicillins and carbapenems presented the largest relative reductions in the ranking of consumption in our area since they were the ones most affected by the DDD changes. Cephalosporins and quinolones increased their share of the total since changes in DDDs affected them less and they continue to be widely consumed. These results corroborate the estimations published by Robertson *et al.*[7]

A limitation of this study is the increase in participating hospitals between 2008 and 2018. This could have caused changes in consumption patterns. However, high-complexity hospitals have participated from the beginning and the use of average consumption from the last 10 years contributes to mitigating the possible selection bias.

In conclusion, the WHO's updates of DDDs have had a significant impact on the measurement of antibacterial consumption. In our region, they have corrected an overestimation of penicillin and carbapenem consumption amounting to 19%.

It is essential to bear these findings in mind for an accurate assessment of temporal trends and benchmarking.

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Transparency declarations

None to declare.

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