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The use of national-level data to describe trends in intramammary antimicrobial usage on Irish dairy farms from 2003 to 2015

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ABSTRACT

In this study, we used national-level data to describe trends in on-farm intramammary antimicrobial usage in Ireland from 2003 to 2015. We calculated actual sales of intramammary tubes and the quantity of active substance sold, by year, product type [lactation or dry cow therapy (DCT)], antimicrobial group, World Health Organization antimicrobial classification, and from 2009 to 2015, prescribing route. We also estimated on-farm usage of lactation and dry cow intramammary antimicrobials using defined daily dose (DDDvet) and defined course dose (DCDvet) calculations, and dry cow coverage. Sales of tubes of antimicrobial for DCT have increased, and the estimated national dry cow coverage in 2015 was 1,022 DCDvet per 1,000 cows per year. An increase has also occurred in sales of teat sealant (2015 sales: 66.7 tubes with teat sealant for every 100 tubes with antimicrobial for DCT). In contrast, the number of tubes of antimicrobial sold for lactation use has decreased to 1,398 DDDvet and 466 DCDvet per 1,000 animals per year. Sales in intramammary tubes with at least one critically important antimicrobial (CIA) have either risen since 2007 (DCT) or fallen (lactation therapy). Increases were observed in both the number of dry cow and lactation tubes containing CIA considered of highest priority for human health. Differences between prescribing routes with respect to CIA usage were observed. This study provides detailed insight into on-farm usage of intramammary antimicrobials in Ireland. It demonstrates positive national progress but also highlights areas for review. In particular, blanket dry cow treatment in Ireland should be reconsidered. It is not possible to investigate farm-level variation in antimicrobial usage from national sales data. In several countries, measurement and benchmarking have been critical to progress in reducing antimicrobial usage in farm animal production. Central collation of data on farm-level antimicrobial use is also needed in Ireland to allow objective measurement and benchmarking of on-farm usage. More generally, standardized indicators to quantify antimicrobial usage in farm animals are urgently needed to allow country-level comparisons.
Key words: intramammary, antimicrobial, critically important, mastitis, Ireland

INTRODUCTION

Mastitis is an important challenge to dairy production internationally. In Ireland, the problem is well understood (More et al., 2012), and considerable work has been undertaken to quantify the economic losses associated with mastitis, both to farmers (Geary et al., 2012) and the processing industry (Geary et al., 2013). In addition to direct monetary concerns, mastitis can adversely affect cow welfare (Medrano-Galarza et al., 2012) and farm management (Jansen et al., 2010), increase the risk of antimicrobial residues (van Schaik et al., 2002), and adversely affect product quality and the international reputation of milk and milk products (More, 2009). A national mastitis control program, CellCheck, was established by Animal Health Ireland (http://animalhealthireland.ie) in late 2010, and farmers now have considerable resources to assist with on-farm mastitis control. In this time, bulk tank somatic cell counts (**BTSCC**), a key measure of udder health, have had a substantial national improvement (Animal Health Ireland, 2016).

In recent years, concern about the use of antimicrobials in animal production has increased. Antimicrobials are a global common good, and prudent use, both in humans and animals, is critical to their long-term effectiveness. In dairy production, antimicrobials are used for a range of animal diseases, but most frequently for either the prevention or treatment of mastitis (Oliver et al., 2011), either lactation or dry cow therapy (**DCT**), as part of a broader mastitis control strategy. Intramammary antimicrobials represent a small proportion of the total quantity of antimicrobials used in farm animal production. In Ireland, for example, 3.8% of veterinary

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antimicrobials sold in 2014 were for intramammary use, either for lactation (0.6%) or dry cow (3.2%) therapy (Health Products Regulatory Authority, 2015).

Methods to quantify on-farm antimicrobial usage are recognized as central to the broader discussion about prudent antimicrobial usage in food production. With such information, it is possible to evaluate temporal trends in usage and to facilitate within-country benchmarking and between-country comparison and studies on drivers for on-farm antimicrobial usage. Considerable progress in this regard has been made in several European countries, including Denmark (Wielinga et al., 2014; DANMAP, 2015) and the Netherlands (Speksnijder et al., 2015; Autoriteit Diergeneesmiddelen, 2016), where farm-level usage data are collected routinely. This is not the case in Ireland, where farm-level usage data are only available as part of defined studies with a primary focus on antimicrobial resistance (Gibbons et al., 2016). However, national sales data are available and have previously provided some insights into farm-level usage (More et al., 2012; Health Products Regulatory Authority, 2015).

Building on earlier work (More et al., 2012), in this study we used national-level data to describe trends in intramammary antimicrobial usage on Irish dairy farms from 2003 to 2015. The results are presented using agreed indicators of on-farm antimicrobial usage to allow inter-country comparison.

MATERIALS AND METHODS

The Data

National Intramammary Antimicrobial Sales Data. Kynetec (Newbury, Berkshire, UK), an international market research company specializing in agriculture and animal health, gathers data on all intramammary sales conducted through each of the 5 main veterinary wholesalers in Ireland. According to Kynetec, this is likely to represent an estimated 85% of all sales of these products in Ireland. We obtained data from Kynetec, summarized for each year from 2003 to 2015 inclusive, of national sales of intramammary products for cows during lactation and at drying off.

In this data set, the reference population was all dairy herds in Ireland, and the unit of interest was the quantity of intramammary antimicrobial product used, expressed either as a quantity of active substance (kg) or number of intramammary tubes. The number of intramammary tubes containing teat sealant was also of interest. The period of interest was 2003 to 2015.

Schedule 8 Prescribing Data. Under national legislation (European Communities, 2007), antimicrobial veterinary medicinal products may only be supplied in Ireland on the basis of a prescription from a registered veterinary practitioner. Further, the animal(s) to which the prescription relates must be under the care of the practitioner. This requires that the practitioner has sufficient knowledge of the animal(s) to form an opinion of the condition of the animal(s) and has visited the animal(s) sufficiently often and recently enough, and at least once in a 12-mo period, to have acquired an accurate picture of the current health, welfare, and disease status of the animal(s). The above-mentioned 12-mo period does not apply to the prescribing of an intramammary antimicrobial agent if the animal belongs to a herd covered by a program meeting the requirements of schedule 8 (within this legislation). Schedule 8, which is unique to Ireland, outlines the requirement of such a program and states that the primary purpose of the program is the prevention and treatment of clinical and subclinical mastitis. The roles and responsibilities of the milk purchaser, the milk supplier (the farmer), and the veterinary practitioner under whose direction the program operates are outlined in schedule 8. Intramammary antimicrobial agents may be prescribed to farmers under either the routine or schedule 8 prescribing routes.

We obtained national data for 2009 to 2015 from the national Department of Agriculture, Food and the Marine on the number and type of intramammary antimicrobial tubes supplied through the schedule 8 prescribing route, both for lactation and DCT. However, anomalies were identified in the data from 2010 for reasons that are not clear. In this study, only the 2011 to 2015 data were used.

Dairy Cow Numbers. Data on the number of dairy cows in Ireland each year between 2003 and 2015 were obtained from Eurostat, the statistical office of the European Union, either directly from their website (data for 2004–2015; http://ec.europa.eu/eurostat) or from the website of the Agricultural and Horticultural Development Board (2003; http://dairy.ahdb.org.uk). These data had been derived from the Irish Animal Identification and Movement database (https://www.agriculture.gov.ie) and collected under Regulation 1165/2008 (European Council, 2008), with dairy cows being defined as "cows kept exclusively or principally for the production of milk for human consumption and/or for processing into dairy products, including cull cows for slaughter (whether fattened or not between last lactation and slaughter)."

Data Analysis

Actual National Sales. The national sales data from Kynetec were analyzed to determine the number of tubes sold, by year and product type (lactation, dry

cow), the number of dry cow intramammary tubes sold, with either active antimicrobial substance or teat sealant, and the quantity of active substance (kg) sold annually, by year, product type, and antibiotic group.

WHO Antimicrobial Classification. The World Health Organization (**WHO**) has classified antimicrobials with respect to importance for human medicine (WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, 2012). Under this system, an antimicrobial that meets both of the following criteria is considered critically important to human health (**CIA**), or highly important if only one criterion is met:

- An antimicrobial agent that is the sole, or one of limited available therapies, to treat serious human disease,
- Antimicrobial agent is used to treat diseases caused by either (1) organisms that may be transmitted to humans from nonhuman sources or (2) human diseases caused by organisms that may acquire resistance genes from nonhuman sources.

The following are relevant to the current study:

- CIA include aminoglycosides (including dihydrostreptomycin, framycetin sulfate, kanamycin, neomycin, and streptomycin), 3rd and 4th generation cephalosporins [including cefoperazone (3rd) and cefquinome (4th)], macrolides (including erythromycin), and penicillins (natural, aminopenicillins, antipseudomonal, including amoxicillin, ampicillin, benethamine penicillin, penethamate hydriodide, procaine benzylpenicillin),
- Highly important antimicrobials for human medicine include 1st and 2nd generation cephalosporins [including cefacetrile, cefapirin, cephalexin, cephalonium (1st)], lincosamides (including lincomycin and pirlimycin hydrochloride), penicillins (antistaphylococcal, including cloxacillin and nafcillin), sulfonamides, dihydrofolate reductase inhibitors and combinations (including sulfadiazine, trimethaprim), and tetracyclines (including oxytetracyclines).

Novobiocin sodium (an aminocoumarin; classified as important for human medicine) was the only other intramammary antimicrobial used in Ireland during the period of interest.

A subgroup of CIA has recently been defined by the WHO, termed highest priority CIA (**HP CIA**), which includes 3rd and 4th generation cephalosporins, glycopeptides, macrolides, quinolones, and potentially carbapenems (Collignon et al., 2016). In this study, only the 3rd and 4th generation cephalosporins and macrolides were used as intramammary antimicrobial products during the study period.

We first classified all intramammary antimicrobials sold in Ireland according to these 2 WHO systems of classification. We then calculated the quantity and percentage of active substance (kg) and the number of tubes, by product type (lactation, dry cow) and WHO antimicrobial classification (CIA, HP CIA).

Prescribing Route. The aforementioned calculations were also conducted on the schedule 8 prescribing data. With the schedule 8 prescribing data, the total number of tubes supplied for lactation therapy and for DCT were available for all milk purchasers (13 milk purchasers in 2011, 12 from 2012 to 2015), whereas finer detail of the number of each type of tube sold (the number of tubes by product) was not always available (these data were not available from milk purchaser A in 2011 to 2014, milk purchaser B in 2011 to 2015, and milk purchaser C in 2014; accounting for between 0.8 and 6.5% of lactation tubes and between 1.5 and 6.2% of dry cow tubes). We assumed that the relative distribution, by WHO classification, of antimicrobials among lactation tubes and among dry cow tubes was the same among milk purchasers for which these finer data were and were not available.

Using both the total sales and schedule 8 prescribing data, we then calculated the quantity and percentage of active substance (kg) and the number of tubes, by product type (lactation, dry cow), WHO antimicrobial classification (CIA, HP CIA), and prescribing route. Separately for each WHO classification, 2 logistic regression models, one for tubes and one for quantity of antimicrobial agents, were developed in SAS version 9.3 (SAS Institute Inc., Cary, NC) to model the proportion of tubes with at least one CIA or HP CIA, or agents that were CIA or HP CIA. The models included year, product type, and prescribing route. Multiple comparisons of the prescribing route by year and product type were accounted for using a Bonferroni correction. Differences were considered to be statistically significant if $P > 0.05$.

Estimated On-Farm Usage. All subsequent calculations were conducted using the national sales data, using indicators of antimicrobial usage as recommended by Collineau et al. (2017). The European Medicines Agency has recently proposed a defined daily dose for animals (**DDDvet**) and the defined course dose for animals (**DCDvet**) for intramammary antimicrobial products in cattle (European Medicines Agency, 2016), drawing on principles presented previously (European Medicines Agency, 2013, 2015). All lactation intramammary products are assigned a DDDvet of 1 unit dose (**UD**, equivalent to an intramammary tube)/teat. All of these products are also assigned a DCDvet of 3 UD/

teat, except for products containing pirlimycin, which have a DCDvet of 8 UD/teat because the number of treatment days is substantially higher than for other lactation intramammary products. For dry cow intramammary products, a DCDvet of 4 UD/udder is assigned.

Therefore, for lactation products, we calculated the number of DDDvet per 1,000 animals per year as

(total number of tubes sold for lactation usage/ assigned DDDvet for each tube)/number of lactating cows at risk of clinical mastitis each year × 1,000,

where total number of tubes sold for lactation usage was assumed to equal the number of lactation tubes recorded by Kynetec/0.85, the assigned DDDvet for each tube was as stated by the European Medicines Agency (2016), and the total number of lactating cows at risk of clinical mastitis each year was considered to be the total number of adult dairy cows. To allow comparison with other studies, this indicator was converted to DDDvet per 1,000 cow-days by dividing DDDvet per 1,000 animals per year by [the mean intercalving interval/365 × (365 – mean length of the dry period)]. From 2008 to 2015 in dairy herds with more than 30 calvings (the only herds and years with available data), the mean intercalving interval was 398 d (Irish Cattle Breeding Federation, 2016). Data on the mean length of the dry period in Ireland were not available, and it was assumed to be 60 d.

The number of DCDvet per 1,000 animals per year was

(total number of tubes sold for lactation usage/ assigned DCDvet for each tube)/number of cows at risk of clinical mastitis each year × 1,000,

where total number of tubes sold for lactation usage was assumed to equal 1/0.85 × the number of lactation tubes recorded by Kynetec, the assigned DCDvet for each tube was as stated by the European Medicines Agency (2016), and the total number of lactating cows at risk of clinical mastitis each year was considered to be the total number of adult dairy cows. To allow comparison with other studies, this indicator was converted to DCDvet per 1,000 cow-days by dividing DCDvet per 1,000 animals per year by [the mean intercalving interval/365 × (365 – mean length of the dry period)].

For dry cow products, we calculated:

The number of DCDvet per 1,000 animals per year as

(total number of dry cow tubes sold/assigned DCDvet value for each tube)/total number of lactating dairy cows eligible for DCT each year × 1,000,

where total number of dry cow tubes sold was assumed to equal 1/0.85 × the number of dry cow tubes recorded by Kynetec, the assigned DCDvet for each tube was as stated by the European Medicines Agency (2016), and the total number of lactating dairy cows eligible for DCT each year was calculated as the total number of adult dairy cows × (1 − the annual replacement rate) × 365/mean intercalving interval. We assumed that DCT was not administered to nulliparous heifers or to cows at the end of their final lactation before culling. From 2008 to 2015 in dairy herds with more than 30 calvings (the only herds and years with available data), the mean annual replacement rate was 20.4% and the mean intercalving interval was 398 d (Irish Cattle Breeding Federation, 2016).

We estimated national DCT coverage (the percentage of lactating cows receiving dry cow intramammary antimicrobial therapy at drying off) after considering the number of lactating dairy cows eligible for DCT (as above), the total number of DCT tubes sold, and varying assumptions about the relationship between Kynetec sales data and on-farm usage.

Data management and analyses were conducted using MS Excel (Microsoft Corp., Redmond, WA). For each measurement over time, a linear regression model was fitted using SAS version 9.3 (SAS Institute Inc.) to test whether there was a linear trend, a quadratic trend, or no change over time. Initially a model that included a linear term (time) and a quadratic term ($time^2$) was tested; however, the quadratic term was dropped if $P > 0.05$ and similarly the linear term (time) was also dropped if $P > 0.05$.

RESULTS

Actual National Sales

Number of Tubes and Quantity of Active Substance. From 2003 to 2015, a decrease ($P = 0.005$, of ~26,000 tubes per year) occurred in the number of tubes of intramammary antimicrobials sold for lactation therapy (Figure 1). During the same period, an increase ($P < 0.001$, of ~106,000 tubes per year) occurred in the number of tubes of intramammary antimicrobials sold in Ireland for DCT, based on sales data collated by Kynetec (Figure 1). An increase also occurred in the number of tubes of teat sealant sold ($P < 0.001$, of ~211,000 tubes per year; Figure 2). From 2011 to 2015,

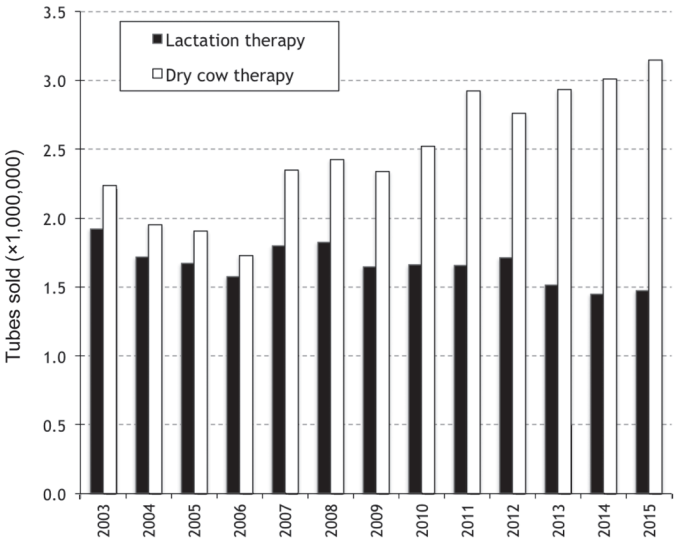

Figure 1. The number of tubes of lactation and dry cow intramammary antimicrobials sold in Ireland from 2003 to 2015, based on sales data collated by Kynetec (Newbury, UK). These sales data represent approximately 85% of actual on-farm usage.

the number of tubes of teat sealant sold each year was 64 to 67% of the total number of tubes of intramammary antimicrobials sold for DCT in the same year.

The quantity of active substance (kg) in intramammary antimicrobial tubes sold annually in Ireland from 2003 to 2015, by product type (lactation and DCT) and antimicrobial group, is shown in Table 1.

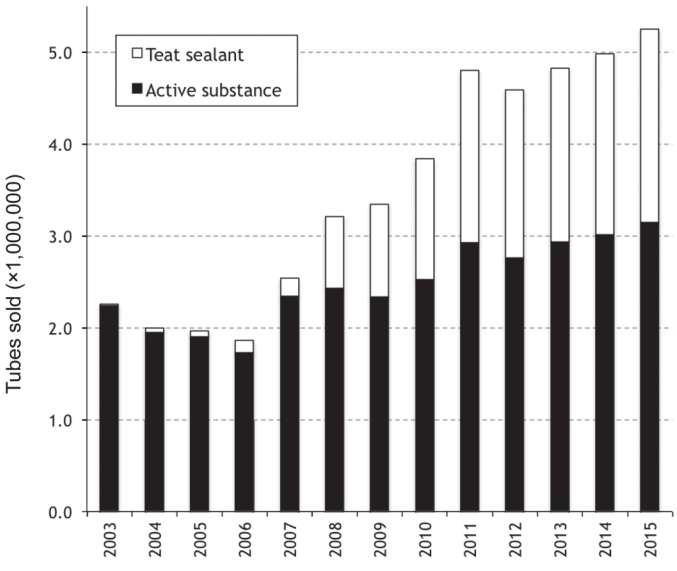

Figure 2. The number of dry cow intramammary tubes sold in Ireland from 2003 to 2015 containing either active antimicrobial substance or teat sealant. These sales data, collated by Kynetec (Newbury, UK), are estimated to represent approximately 85% of actual on-farm usage.

WHO Antimicrobial Classification. All antimicrobials sold were classified as either CIA or highly important for human medicine, except novobiocin (an aminocoumarin), which accounted for 10 and 0% by weight of active substance sold in 2015 for lactation and DCT, respectively (Table 1, Figure 3). In 2015, 6.9 and 5.4% of lactation and DCT tubes contained a HP CIA, respectively. Of the HP CIA, erythromycin (a macrolide) was used from 2003 to 2005 only, whereas cefoperazone (a 3rd generation cephalosporin) was used throughout the study period (2003–2015) for lactation therapy, and cefquinome (a 4th generation cephalosporin) throughout the study period and from 2009 in increasing quantities, for lactation and DCT, respectively (Table 1).

From 2003 to 2015, a decrease ($P = 0.002$, by ~28,000 tubes per annum) occurred in the number of lactation tubes sold with a CIA (Figure 3a), but no change ($P = 0.240$) occurred in the number of lactation tubes sold with no CIA (Figure 3a). During the same period, an increase ($P < 0.001$) was observed in the number of lactation tubes (an increase of ~8,000 per year) sold containing HP CIA (Figure 3b). From 2003 to 2015, the number of tubes sold annually in Ireland of dry cow antimicrobials with at least one CIA initially fell but has been increasing from 2007 (a quadratic curve, with an annual increase from 2007 of ~31,000 tubes per year, $P = 0.036$). The number of dry cow tubes with no CIA increased ($P < 0.001$) from 2003 to 2015, by ~87,000 per year (Figure 3a). From 2003 to 2015, an increase ($P < 0.001$) was observed in the number of dry cow tubes (an increase of ~18,000 per annum) sold containing HP CIA (Figure 3b).

Generally similar patterns were observed when considering the quantity of active substance sold annually. With respect to the quantity of active substance sold for lactation therapy, a decrease ($P < 0.001$) occurred in the sale of CIA from 2003 to 2015, but no change was observed among either highly important ($P = 0.508$) or other ($P = 0.632$) antimicrobials (Supplemental Figure S1a; https://doi.org/10.3168/jds.2016-12068). During the same period, an increase ($P < 0.001$) occurred in the quantity of antimicrobials with HP CIA that were sold (Supplemental Figure S1b; https://doi.org/10.3168/jds.2016-12068). With respect to the quantity of active substance sold for DCT, an initial fall occurred, then an increase from 2007 (a quadratic curve, with an annual increase from 2007 of ~12,000 tubes per year, $P = 0.012$) in CIA (Supplemental Figure S1a; https://doi.org/10.3168/jds.2016-12068). From 2003 to 2015, an increase ($P = 0.001$) occurred in the sales of highly important antimicrobials, but no change ($P = 0.111$) for other antimicrobials. From 2003 to 2015, an increase ($P < 0.001$) occurred in the quantity of active substance

Table 1. The quantity of active substance (kg) in intramammary antimicrobial tubes sold annually in Ireland from 2003 to 2015, by product type (lactation and dry cow therapy) and antibiotic group

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Lactation therapy													
Aminocoumarin	56.5	50.3	45.4	40.6	48.7	43.0	41.5	51.6	51.1	50.4	52.9	43.3	44.5
Aminoglycosides	269	238	227	206	230	260	219	169	171	183	191	163	172
Cephalosporins													
1st generation	85.5	80.0	73.8	70.9	68.5	77.7	74.7	89.0	89.4	90.4	85.7	76.8	79.1
3rd generation	1.0	1.3	1.8	1.4	2.2	2.5	1.8	2.0	1.6	1.5	1.3	1.1	1.2
4th generation	2.0	2.1	3.6	3.6	4.0	4.5	4.4	8.3	9.2	9.8	10.1	7.9	7.3
Lincosamides	10.5	5.4	4.6	3.6	3.4	4.7	3.4	3.9	3.3	2.7	3.8	4.3	4.2
Macrolides	0.9	0.6	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Penicillins													
Narrow spectrum													
β-Lactamase sensitive	120	104	99.8	89.2	102	108	91.6	55.2	55.2	63.1	70.2	60.6	64.0
Penicillinase-resistant	3.1	2.7	3.1	3.8	2.3	1.7	1.6	2.9	3.1	2.8	2.4	1.6	1.7
Moderate spectrum	1.1	1.0	1.2	1.4	0.9	0.6	0.6	1.1	1.2	1.1	0.9	0.6	0.7
Broad spectrum	77.7	69.5	71.2	73.4	84.4	81.6	81.6	99.8	96.3	95.7	47.8	72.5	70.7
Sulfonamides	1.7	1.5	1.2	0.6	17.1	5.0	3.1	3.7	3.3	2.1	3.3	1.7	1.4
Tetracyclines	3.6	3.5	4.1	3.8	4.6	11.9	4.4	0.0	0.0	0.0	0.0	0.0	0.0
Subtotal	632	560	537	498	567	601	528	487	485	503	470	434	447
Dry cow therapy													
Aminocoumarin	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	55.7	45.4	40.3	34.9	35.8	92.6	67.6	39.9	41.5	105	127	147	148
Cephalosporins													
1st generation	147	155	164	170	213	271	276	297	327	415	426	478	481
3rd generation													
4th generation	0.0	0.0	0.0	0.0	0.0	0.0	1.1	5.7	22.8	22.7	25.6	22.1	25.3
Lincosamides													
Macrolides													
Penicillins													
Narrow spectrum													
β-Lactamase sensitive	203	162	144	115	128	138	137	167	177	106	134	132	160
Penicillinase-resistant	652	529	510	445	675	637	539	507	580	482	524	483	500
Moderate spectrum	160	146	144	132	205	145	119	137	140	135	123	126	128
Broad spectrum													
Sulfonamides													
Tetracyclines													
Subtotal	1,218	1,038	1,003	896	1,256	1,284	1,139	1,153	1,288	1,266	1,359	1,388	1,443
Total	1,850	1,598	1,540	1,395	1,823	1,885	1,667	1,640	1,773	1,769	1,829	1,821	1,889

with HP CIA sold for DCT (Supplemental Figure S1b; https://doi.org/10.3168/jds.2016-12068).

Estimated On-Farm Usage

Usage by Prescribing Route. The estimated percentage of tubes supplied through the schedule 8 prescribing route did not change between 2011 and 2015, either for lactation ($P = 0.252$) or dry cow ($P = 0.139$) therapy (Figure 4). In 2015, the schedule 8 prescribing route was used extensively, representing 45 and 51% of lactation and dry cow tubes, respectively.

Different patterns were observed when comparing prescribing routes with respect to CIA (Table 2) and HP CIA (Table 3). With DCT, the odds of prescribing CIA was greater, and of HP CIA much greater, through the routine compared with the schedule 8 prescribing route. In 2015, for example, the odds of prescribing a tube with at least one CIA or at least one HP CIA by the routine route was 2.09 and 19.3 times greater, respectively, compared with those prescribed by schedule 8. For lactation therapy, significantly more CIA were prescribed through schedule 8 compared with the routine prescribing route, whereas the converse was true

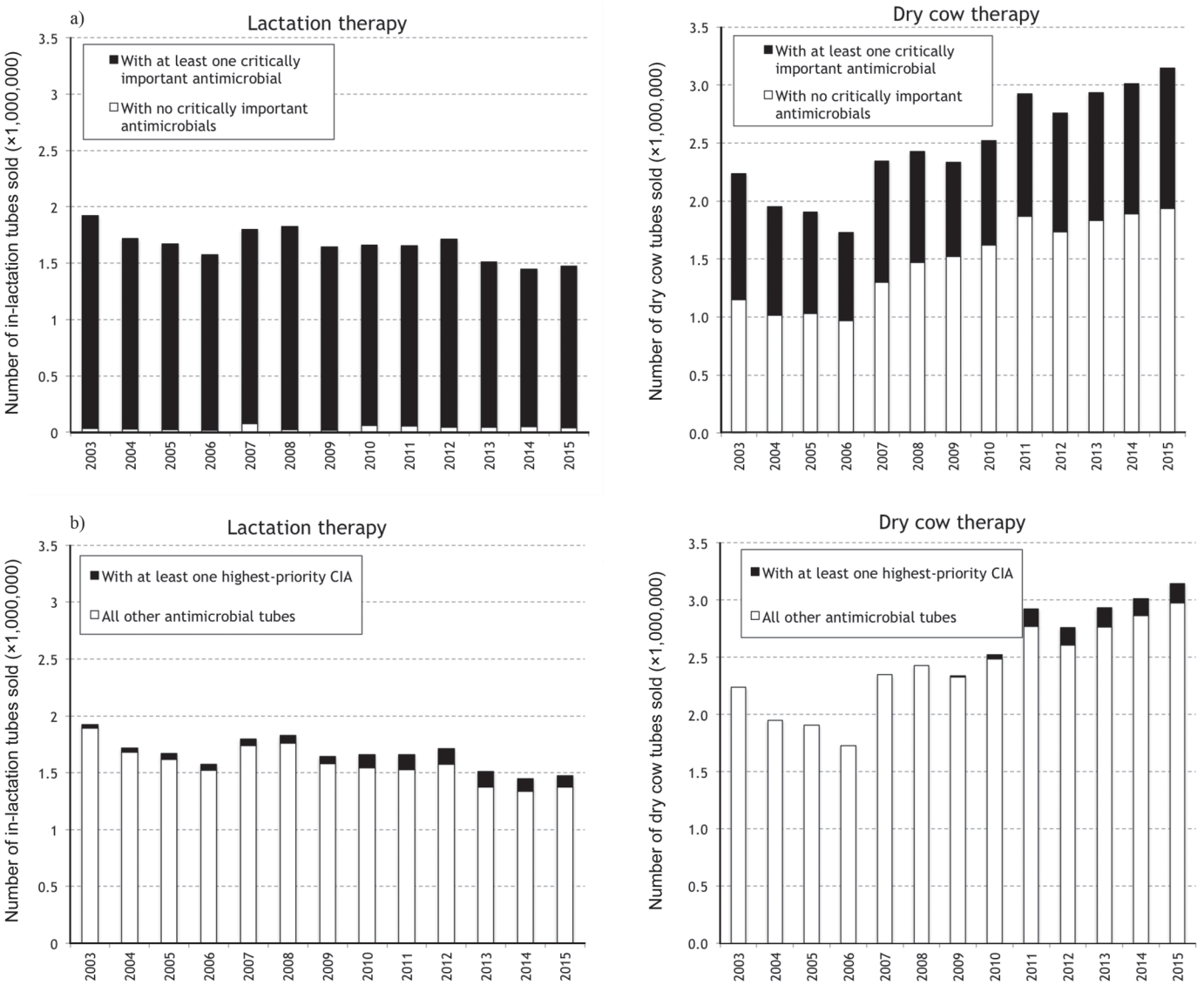

Figure 3. Number of tubes of dry cow and lactation intramammary antimicrobials for lactation (left) and dry cow (right) therapy, sold annually in Ireland from 2003 to 2015, containing either (a) at least one or no critically important antimicrobials (CIA) for human medicine and (b) at least one or no highest priority critically important antimicrobials for human medicine. The figures are based on sales data collated by Kynetec (Newbury, UK).

Table 2. Comparison of prescribing route for critically important antimicrobials in Ireland from 2011 to 2015, by method of measurement (number of tubes, kg of active compound), product type (dry cow and lactation therapy), and year

Item	Year	Prescribing route		Odds ratio[1]	95% Confidence limits		*P*-value[2]
		Routine	Schedule 8		Lower	Upper	
Number of tubes, % of tubes with at least one critically important antimicrobial							
Dry cow therapy							
	2011	45.5	28.8	2.07	2.06	2.07	<0.001
	2012	46.4	31.2	1.90	1.90	1.91	<0.001
	2013	46.0	29.8	2.01	2.00	2.02	<0.001
	2014	44.7	29.7	1.92	1.91	1.93	<0.001
	2015	47.3	30.0	2.09	2.09	2.10	<0.001
Lactation therapy							
	2011	96.2	97.8	0.57	0.56	0.58	<0.001
	2012	97.4	97.9	0.82	0.80	0.83	<0.001
	2013	97.1	97.4	0.90	0.88	0.92	<0.001
	2014	96.0	98.1	0.46	0.45	0.47	<0.001
	2015	96.0	99.2	0.21	0.20	0.21	<0.001
Quantity of antimicrobials, % of critically important among all antimicrobials							
Dry cow therapy							
	2011	50.7	18.2	4.63	4.60	4.67	<0.001
	2012	52.4	19.2	4.62	4.59	4.66	<0.001
	2013	46.5	18.3	3.87	3.85	3.90	<0.001
	2014	44.5	18.9	3.45	3.42	3.47	<0.001
	2015	47.9	19.3	3.84	3.81	3.87	<0.001
Lactation therapy							
	2011	72.4	75.8	0.84	0.83	0.85	<0.001
	2012	74.8	75.6	0.96	0.94	0.97	<0.001
	2013	73.5	74.6	0.95	0.94	0.96	<0.001
	2014	74.5	76.2	0.92	0.90	0.93	<0.001
	2015	69.1	80.6	0.54	0.53	0.54	<0.001

[1]The reference group is the schedule 8 prescribing route. Therefore, an odds ratio of 2 is interpreted as the routine prescribing route having double the odds of prescribing a critically important antimicrobial compared with the schedule 8 route.

[2]Adjusted using the Bonferroni method.

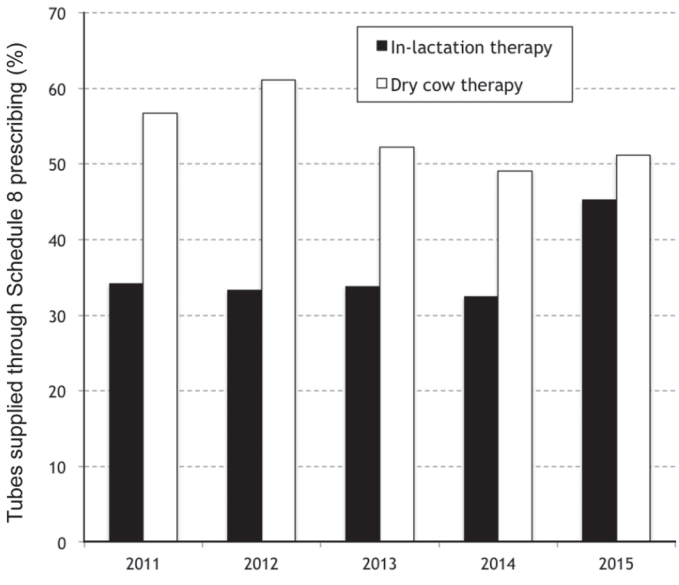

Figure 4. Estimated percentage of tubes of intramammary antimicrobials supplied through the schedule 8 prescribing route, by year and purpose. The Kynetec (Newbury, UK) data were assumed to represent 85% of actual on-farm usage.

with HP CIA. Again using 2015 as an example, the odds of prescribing a tube with at least one CIA or at least one HP CIA by the routine route was 0.21 and 2.81 times as likely, respectively, compared with those prescribed by schedule 8.

Estimated Defined Daily Dose for Animals, Defined Daily Course for Animals. The estimated on-farm antimicrobial usage of lactation and dry cow intramammary antimicrobials, using defined daily dose and defined course dose calculations, is presented in Table 4. The estimated usage of lactation antimicrobials has fallen from 1,993 to 1,398 DDDvet per 1,000 animals per year from 2003 to 2015, respectively (a quadratic curve, with an annual decrease from 2008 of ~92 DDDvet per 1,000 cows per year, $P < 0.001$), and from 663 to 466 DCDvet per 1,000 animals per year from 2003 to 2015, respectively (a quadratic curve, with an annual decrease from 2008 of ~30 DCDvet per 1,000 cows per year, $P < 0.001$). From 2003 to 2015, an increase ($P < 0.001$) occurred in the estimated usage of antimicrobials in DCT, rising from 794 to 1,022 DCDvet per 1,000 animals per year from 2003 to 2015, respectively.

Estimated Dry Cow Coverage. The estimated national coverage of DCT in Ireland from 2003 to 2015, based on varying assumptions about the relationship between Kynetec sales data and on-farm usage of intramammary antimicrobials, is presented in Figure 5. The estimated dry cow coverage has increased ($P < 0.001$), by between 2.9% (sales data assumed to represent 90% of all on-farm usage) and 3.2% (sales data assumed to represent 80% of all on-farm usage) for each year between 2003 and 2015, reaching approximately 100% coverage during at least the last 6 yr of the study period.

DISCUSSION

This study provides important insights into intramammary antimicrobial usage in Ireland, relating to both lactation and dry cow therapies. Farm-level data are not currently available in Ireland, and therefore this study was conducted solely using national-level sales and prescribing data.

These results highlight reducing usage of lactation therapies in Ireland in recent years (Table 1), from a high of 2,099 DDDvet per 1,000 animals per year (equivalent to 6.0 DDDvet per 1,000 cow-days and 2.0 DCDvet per 1,000 cow-days) in 2008 to 1,398 DDDvet per 1,000 animals per year (4.2 DDDvet per 1,000 cow-days, 1.4 DCDvet per 1,000 cow-days) in 2015 (Table 4). The 2015 figures compare favorably to those reported in other important dairying countries. In the Netherlands, the estimated mean usage of lactation therapy on 94 study farms was 1.45 animal-defined daily doses (**ADDD**; synonymous with DDDvet) per cow, or 1,450 DDDvet per 1,000 cows per year (Kuipers et al., 2016). The estimated mean usage of these therapies on study farms was 6.30 defined daily dose animals (synonymous with DDDvet) per 1,000 cow-days, or 1,922 DDDvet per 1,000 cows per year in Belgium (Stevens et al., 2016b). In Canada, the antimicrobial drug use rate (synonymous with DDDvet) during lactation was 3.52 animal defined daily doses per 1,000 cow-days or 1,074 DDDvet per 1,000 cows (Saini et al., 2012). On conventional Wisconsin farms, the treatment of clinical mastitis contributed 2.02 defined daily doses (synonymous with DDDvet) per cow per year, equivalent to 2,013 DDDvet per 1,000 cows per year (Pol and Ruegg, 2007). We can only speculate at the reasons for the observed fall in on-farm antimicrobial usage during lactation in Ireland. It should be noted that the national BTSCC has improved substantially in recent years, coincident with the introduction of CellCheck, which has considerably raised awareness of appropri-

Table 3. Comparison of prescribing route for highest priority critically important antimicrobials in Ireland from 2011 to 2015, by method of measurement (number of tubes, kg of active compound), product type (dry cow, lactation), and year

Item	Year	Prescribing route		Odds ratio[1]	95% Confidence limits		P-value[2]
		Routine	Schedule 8		Lower	Upper	
Number of tubes, % of tubes with at least one highest priority critically important antimicrobial							
Dry cow therapy[3]							
	2014	9.5	0.1	85.5	81.91	89.23	<0.001
	2015	10.4	0.6	19.3	18.89	19.62	<0.001
Lactation therapy							
	2011	8.4	6.6	1.30	1.29	1.32	<0.001
	2012	8.6	6.7	1.32	1.30	1.33	<0.001
	2013	10.5	6.9	1.57	1.55	1.59	<0.001
	2014	8.0	6.6	1.23	1.22	1.25	<0.001
	2015	9.6	3.6	2.81	2.77	2.85	<0.001
Quantity of antimicrobials, % of highest priority critically important among all antimicrobials							
Dry cow therapy[3]							
	2014	3.5	0.03	107.3	95.78	120.3	<0.001
	2015	3.8	0.2	23.8	22.67	25.08	<0.001
Lactation therapy							
	2011	2.5	1.8	1.44	1.38	1.49	<0.001
	2012	2.7	1.5	1.80	1.73	1.87	<0.001
	2013	2.8	1.7	1.66	1.59	1.72	<0.001
	2014	2.3	1.6	1.45	1.39	1.51	<0.001
	2015	3.0	0.9	3.48	3.32	3.64	<0.001

[1]The reference group is the schedule 8 prescribing route. Therefore, an odds ratio of 2 is interpreted as the routine prescribing route having double the odds of prescribing a high priority critically important antimicrobial compared with the schedule 8 route.

[2]Adjusted using the Bonferroni method.

[3]In 2011 to 2013, there was either little or no usage of highest priority critically important antimicrobials among dry cow therapy prescribed under schedule 8.

Table 4. Estimated on-farm antimicrobial usage of lactation and dry cow intramammary antimicrobials in Ireland from 2003 to 2015, using defined daily dose (DDDvet) and defined course dose (DCDvet) calculations[1]

Item	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Lactation antimicrobials													
Defined daily dose													
DDDvet per 1,000 animals per year	1,993	1,800	1,976	1,812	2,081	2,099	1,893	1,940	1,882	1,900	1,644	1,511	1,398
DDDvet per animal per year	2.0	1.8	2.0	1.8	2.1	2.1	1.9	1.9	1.9	1.9	1.6	1.5	1.4
DDDvet per 1,000 cow-days	6.0	5.4	5.9	5.4	6.3	6.3	5.7	5.8	5.7	5.7	4.9	4.5	4.2
Defined course dose													
DCDvet per 1,000 animals per year	663	600	658	604	693	699	631	646	627	633	548	503	466
DCDvet per 1,000 cow-days	2.0	1.8	2.0	1.8	2.1	2.1	1.9	1.9	1.9	1.9	1.6	1.5	1.4
Dry cow antimicrobials													
Defined course dose													
DCDvet per 1,000 animals per year	794	700	771	681	930	955	921	1,009	1,138	1,048	1,092	1,076	1,022

[1]It is assumed that the Kynetec sales data represent 85% of all on-farm usage.

ate mastitis control strategies. It is possible, therefore, that the observed decrease in usage may be related to both a reducing incidence in clinical and subclinical mastitis and to more prudent on-farm antimicrobial usage. Further investigation of this issue is warranted. It is important to note that *Staphylococcus aureus* is generally the pathogen most commonly associated with IMI in Ireland (More et al., 2012), although subsequent work has shown that environmental pathogens, such as *Streptococcus uberis* and *Escherichia coli* also present a considerable challenge (Keane et al., 2013). The efficacy of mastitis therapy for chronic *S. aureus* infection during lactation is extremely low, leading to very low cure rates following treatment (Oliver et al., 2011). Therefore, despite ongoing reductions in usage, it is possible that there remains an overreliance on the use of antimicrobials in Ireland in situations where the efficacy of treatment is low (More et al., 2012).

Over the last 6 yr at least, the estimated national coverage of DCT has been close to 100% (Figure 5). This follows a substantial rise since 2007 both in the number of dry cow tubes (Figure 1) and the quantity of active substance (Table 1) sold. Concurrently, a significant increase has also occurred over time in the use of teat sealant (Figure 2). It is important to note that teat sealants are being used in addition to (rather than as a substitute for) antimicrobial therapy, given

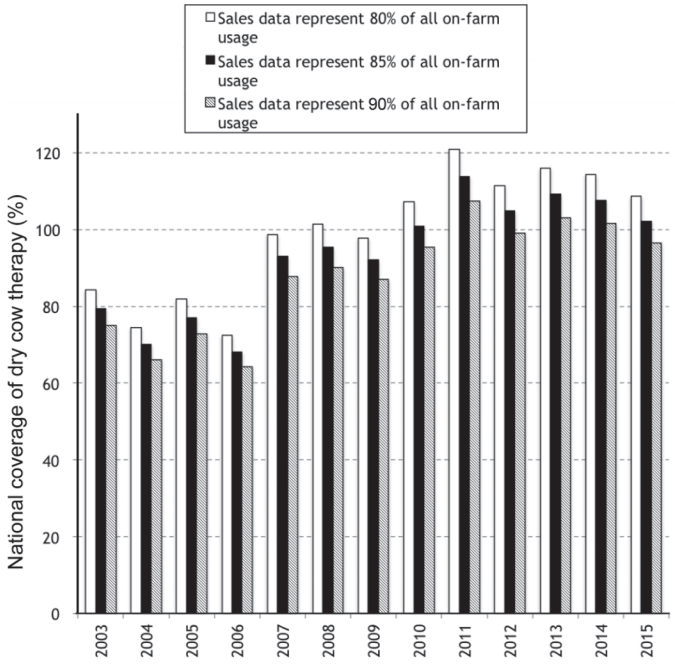

Figure 5. Estimated national coverage of antimicrobial dry cow therapy in Ireland from 2003 to 2015, using different assumptions about the relationship between Kynetec (Newbury, UK) sales data and on-farm usage of dry cow intramammary antimicrobials.

the near universal use of antimicrobial products for DCT observed. In several years, the estimated national coverage exceeded 100%, for reasons that are unclear. We caution, as highlighted below, that all estimates of on-farm usage need to be interpreted with care given the assumptions made during these calculations. The on-farm usage of dry cow antimicrobial therapy is substantially greater than other countries with recently published data. In the current study, the estimated DCDvet in Ireland varied between 681 (in 2006) and 1,138 (2011) per 1,000 animals per year, and was 1,022 per 1,000 animals per year in 2015 (Table 4). In a recent Dutch study, the estimated mean usage of DCT on 94 study farms from 2005 to 2012 was 2.57 ADDD per cow per year, equivalent to 643 DCDvet per 1,000 cows per year (Kuipers et al., 2016). Considerable farm-level variation was present, with almost 40% of farms using less than this.

Although the adoption of DCT in Ireland was encouraged over the last decade for the purpose of improving udder health, blanket DCT should be reconsidered, both in light of these results and for several other reasons. In recent years, substantial national progress has been made in reducing BTSCC, and consequently there is an increasing number of farms where selective DCT would be an option. Further, the unjustified use of blanket DCT is at odds with growing concerns about on-farm antimicrobial usage (Biggs et al., 2016). Nonetheless, recent studies have highlighted some of the challenges related to selective DCT. Selection based on SCC at the last milk recording before drying off gives a substantial reduction in antimicrobial use, but leads to an increase in clinical mastitis, subclinical mastitis, and culture-positive quarters (Scherpenzeel et al., 2014). In contrast, no adverse effect was observed on postcalving IMI or clinical mastitis (Cameron et al., 2014) or on milk production or SCC (Cameron et al., 2015) in the subsequent lactation when Petrifilm-based on-farm culture systems were used to allow targeting of selective DCT. The use of teat sealant, in place of an antimicrobial, is also an option for selective DCT. The incidence of IMI and clinical mastitis in dairy cows during early lactation was considerably reduced following the application of internal teat sealants at drying off either alone or with the addition of antimicrobials, based on a recent meta-analysis by Rabiee and Lean (2013). Industry-agreed guidelines for selective dry cow treatment under Irish conditions are available (CellCheck, 2011). In Ireland, key challenges, relevant to selective dry cow treatment, include milk recording (to generate individual cow data) and hygienic practices at drying off and subsequently. Whole-herd milk recording was conducted on 39% of herds (comprising 52% of dairy cows) in 2015 (ICAR, 2016); however, the average number of tests per lactation was relatively low (4.40 and 4.49 in 2014 and 2015, respectively). This presents a challenge for the adoption of selective dry cow treatment, where limited (or no) individual cow data are available to inform decision making.

This work highlights the widespread use of CIA (Figure 3a, Supplemental Figure S1a; https://doi.org/10.3168/jds.2016-12068) both to treat and prevent mastitis in dairy cows in Ireland. Although the use of HP CIA is limited, a significant increase has occurred from 2003 to 2015 in the number of tubes for both lactation and DCT that contain at least one HP CIA (Figure 3b, Supplemental Figure S1b; https://doi.org/10.3168/jds.2016-12068). In 2015, 38.5 and 5.4% of tubes for DCT contained a CIA or a HP CIA, respectively. The equivalent figures in 2015 for lactation therapy were 97.4 and 6.9%, respectively. Focus should primarily be placed on HP CIA, which are of highest priority for human health, and were identified specifically "to allow stakeholders in the agriculture sector and regulatory agencies to focus risk management efforts on drugs used in food animals that are the most important to human medicine" (Collignon et al., 2016). Macrolides are classified as HP CIA by the WHO (WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, 2012), but not by the European Medicines Agency based on their degree of risk to people due to resistance development following use in animals (European Medicines Agency, 2014). If the classification of macrolides were changed, this would not affect the results of the current study, noting that all HP CIA in intramammary antimicrobial products in Ireland since 2006 have been 3rd and 4th generation cephalosporins (Table 1). Widespread use of HP CIA in dairy cattle has been reported elsewhere. For example, Stevens et al. (2016b) recently reported widespread use of 3rd and 4th generation cephalosporins and fluoroquinolones in dairy farms in Belgium, but with considerable farm-level variation. However, there are also examples of national action to successfully restrict the use of HP CIA in cattle production, specifically as a consequence of public health concerns. In Denmark, the use of 3rd and 4th generation cephalosporins in intramammary applications has fallen over 10-fold between 2007 and 2014, to 21,000 defined animal daily doses (conversion to DDDvet from aggregated data is not possible). This was partly a consequence of public concern, particularly with respect to a broader debate and information about the development of extended-spectrum β-lactamases, and the introduction of legislation requiring testing for antimicrobial resistance in cases where antimicrobial agents other than simple penicillins are prescribed for

mastitis (DANMAP, 2011). Denmark also has differential taxes on the sales of antimicrobials and other medicines for veterinary use (vaccines: no tax; penicillins, simple and narrow spectrum: 0.8% tax; 3rd and 4th generation cephalosporins: 10.8% tax; DANMAP, 2014). In the Netherlands, a combination of compulsory and voluntary actions with clear reduction goals were introduced in recent years, including substantial restriction in the use of 3rd and 4th generation cephalosporins and fluoroquinolones in farm animals (Speksnijder et al., 2015).

In Ireland, antimicrobial agents are available only by veterinary prescription. With intramammary products, 2 prescribing routes are allowed; the routine and schedule 8 prescribing routes. With this latter route, there is no requirement for a herd visit by the prescribing veterinarian at least every 12 mo if the herd is covered by a mastitis prevention and treatment program as outlined in the relevant legislation (European Communities, 2007). In this study, we highlight the similar importance of both of these 2 routes, in terms of the number of tubes sold (Figure 4). Further, differences between prescribing routes with respect to CIA usage were observed. In general, CIA and HP CIA were less likely to be prescribed through schedule 8 prescribing compared with the routine prescribing route, the exception being CIA in lactation therapy. The difference between the 2 prescribing routes was most marked with HP CIA in DCT: during 2014 and 2015, HP CIA were present in between 9.5 and 10.4% of these tubes through the routine prescribing route compared with 0.1 to 0.6% of tubes through schedule 8 prescribing (Table 3). Given the importance of schedule 8 prescribing in Ireland, as evident from this study, further work is justified to better understand factors associated with veterinary prescribing under these 2 routes.

This study was mainly conducted using national sales data. Although such data are centralized and readily available, they generally do not allow for the distribution of consumption in different animal species, weight groups, or production types (European Medicines Agency, 2013). In contrast to most antimicrobial products, however, intramammary tubes are generally used as intended (that is, for intramammary application), except for occasional use for the treatment of pink eye in cattle. Therefore, sales can be reasonably extrapolated to on-farm usage as intended. We caution, however, that the on-farm usage estimates should be interpreted with caution. Several assumptions were needed when estimating on-farm usage from national sales data, including the number of lactating dairy cows at risk of clinical mastitis, the number of lactating dairy cows eligible for DCT, and the relationship between Kynetec sales data and on-farm usage. Concerning the number of animals at risk of clinical mastitis or eligible for DCT, we relied on available national data, but noting that data about the annual replacement rate and intercalving interval were limited to 2008 to 2015 and to herds with at least 30 calvings. We conducted a sensitivity analysis, as presented in Figure 5, to highlight the effect on national coverage of DCT of variations in the relationship between Kynetec sales data and on-farm usage. We had limited access to the remaining sales data that were not captured by Kynetec, specifically the sales of lactation and dry cow tubes available in the Irish market during the study period, and within this the percentage of tubes that contained an HP CIA. The Kynetec and non-Kynetec data are similar in this regard, providing confidence that the Kynetec data are representative of all intramammary antimicrobials sold in Ireland.

There has been considerable confusion in the literature concerning measurement of on-farm antimicrobial usage, with both methodology and terminology. This issue is less problematic for intramammary antimicrobial usage in comparison to other administration routes. Nonetheless, as illustrated previously, the measurements used to quantify lactation usage in Belgium (defined daily dose animals), Canada (antimicrobial drug use rate), the Netherlands (ADDD), and the United States (defined daily doses) can be compared, whereas those from Denmark (defined animal daily doses) cannot. Further, differing approaches have been used when quantifying DCT usage. In this study, we measured on-farm usage of antimicrobials for DCT using defined course dose for animals (DCDvet), noting that a single application provides long-term action during the dry period and represents a therapeutic course. This approach is logical, but at odds with recent publications where the levels of DCT have previously been expressed in terms of DDDvet (Kuipers et al., 2016; Stevens et al., 2016b). For this reason, we conducted back-calculations to allow comparison. The lactation sales data were used to estimate antimicrobial usage (DDDvet).

This study has highlighted the urgent need for standardized indicators for quantification of antimicrobial usage in farm animals, to allow country-level comparisons. Collineau et al. (2017) have recently addressed this issue in a comprehensive review, and have suggested technical units, indicators, and data sources to address 4 different study objectives, including monitoring usage trends over time, comparing usage between species or countries, benchmarking between farms, and studying the association between antimicrobial usage and resistance. The recommendations of Collineau et al. (2017) were followed in the current study.

CONCLUSIONS

This study provided detailed insight into on-farm usage of intramammary antimicrobials in Ireland. It demonstrates positive national progress, particularly with respect to lactation antimicrobial usage, but also highlights areas for review and further research. In particular, blanket dry cow treatment in Ireland should be reconsidered. It is not possible to investigate farm-level variation in antimicrobial usage from national sales data. Several studies have investigated farm-level usage using data collected from drug sales (Kuipers et al., 2016) or garbage can audits (Stevens et al., 2016a,b). Farm-level antimicrobial usage data are now routinely collected in several European countries, including Denmark (Wielinga et al., 2014; DANMAP, 2015) and the Netherlands (Speksnijder et al., 2015; Autoriteit Diergeneesmiddelen, 2016), where it is central to efforts to reduce antimicrobial usage in farm animal production. Central collation of data on farm-level antimicrobial use is also needed in Ireland to allow objective measurement and benchmarking of on-farm usage. More generally, standardized indicators to quantify antimicrobial usage in farm animals are urgently needed to allow country-level comparisons.

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