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Investigation of the risk of consuming marketed milk with antimicrobial residues in Kenya

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Abstract

The risk of consuming marketed milk containing antimicrobial residues was investigated by testing 854 unpasteurized and 110 pasteurized milk samples collected from contrasting locations, market outlets and consumer households in Kenya during 1999 and 2000. The Charm-AIM screening kit used detected antimicrobial residues in up to 16% of marketed milk samples, suggesting an average risk of exposure by consumers of up to five times every month. Higher prevalence levels of the residues were mainly associated with samples obtained lower in the market chain before bulking. Agreement between the Charm-AIM and Charm-SL test, that was used to specifically confirm the presence of β-lactams and tetracyclines, was poor beyond 72 h following drug administration due to differences in detectable limits of the tests.

Keywords: Antimicrobial residues; Marketed milk; Kenya

1. Introduction

Residues of antimicrobial agents (antibacterials and antibiotics) used in animal health practice can be detected in various animal tissues for some duration following therapy, and are usually attributed to non-observance of withdrawal periods before sale of animal source food (Roundant & Moreitain, 1990; Suliman, 1976). The residues may also occur following feeding feeds contaminated with antimicrobials (McEvoy, Mayne, Higgins, & Kennedy, 2000) or direct addition of antimicrobial agents to preserve milk as some undocumented reports in Kenya claim. Drug residues are of concern to human health due to their association with varying degrees of allergies from mild skin rashes to angio-oedema and life-threatening anaphylaxis (Oslon & Sanders, 1975), drug resistance and the resultant long-term development of 'super bugs' immune to attack by common, less expensive antimicrobials (Mol, Boer, Demmers, Schut, & Vincentie, 1978; Nijsten, London, Van de Bogaard, & Stobberingh, 1996; Swartz, Jooste, & Novello, 1984). Other adverse health effects arising from tetracycline residues that have been known for a long time include gastrointestinal disturbance, liver damage, and yellowing of teeth and dental hypoplasia (Moffit, Cooley, Olsen, & Neffeman, 1970; Schultz, Adamson, Workman, & Norman, 1963).

In common with many tropical developing countries, the extent of this problem in Kenya has not been quantified in the past. As a result, policy makers remain largely unaware of the extent of the problem and no quality assurance programmes are in place to prevent sales of animal source foods that may contain antimicrobial residues. Implementing such programmes poses a major challenge for countries such as Kenya where informal food sales are common. Kenya provides an ideal environment in Africa to begin to study this problem due to the high milk consumption per-capita which, at approximately 90 kg liquid milk equivalent per

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annum, is 4–5 times greater than for other countries in the region; and, over 80% of the sales are direct by producers to consumers or via numerous small-scale milk market agents.

Reported occurrences of drug residues in milk and other foods destined for the market in various countries vary widely. They are low or non-existent in countries where quality assurance programmes are effective, but vary from low to high in other countries. For example, in Poland, Rybinska, Postupolski, and Szczsena (1995) found 13–22% of raw milk and 11–20% of powdered milk samples contained antibiotic residues. Investigations in Hyderabad State in India by Sundershan and Bhat (1995) found 9% of marketed bulk milk samples and as high as 73% of milk samples obtained from individual animals at farm level had oxytetracycline residues, which perhaps indicates some dilution effect of bulking on residue concentration. Cook, Katz, and Meara (1976) reported the presence of penicillin residues up to 3% of bulk milk supplied to Johannesburg, South Africa.

In Kenya, indications are that the prevalence of antimicrobial residues in milk above recommended maximum residue limits (MRLs) has been low in the past but has increased recently. During the period when formal milk sales in Kenya was monopolized by one major parastatal, the Kenya co-operative creameries, a study by Chewulukie (1978) found penicillin in only 1% of milk deliveries for processing. Ombui (1994) failed to detect any antibiotic residues in bulked and non-bulked milk received at dairy cooperatives in Kiambu district, due to high level of awareness on withdrawal periods among farmers delivering the milk. More recent studies in Kenya have, however, found higher prevalences of antimicrobial residues in milk and meat samples. For example, 11% of raw bulk milk samples sold in Nakuru were recently found to have penicillin-G residues (Shitandi & Sternesjö, 2001) and as high as 20% of meat samples collected from slaughterhouses around Nairobi were demonstrated to have tetracycline residues above recommended MRLs (Muriuki, Ogara, Njeruh, & Mitema, 2001).

The pharmacokinetic and toxicological bases for setting the international regulatory standards have been recently summarized by Anadon and Martinez-Larranaga (1999). It will suffice to mention here that the acceptable daily intake (ADI) represents the total drug residues and metabolites that can be safely consumed through out one's life. ADI indices are usually established based on the determination of a no observable effect level (NOEL) and application of a safety factor. The ADI approach was developed to take account of effects based on classical toxicity studies in laboratory animals, using NOEL for the most sensitive toxicological parameter in the most sensitive species of experimental animal as a starting point (WHO, 1989). The ADI is calculated by dividing the NOEL by a suitable safety factor, usually 100. MRLs are based on the residue profile and its decline in the treated animal.

This paper describes prevalence levels of antimicrobials in marketed milk above recommended MRLs and the risk of consuming such milk, based on test results obtained using the Charm-AIM and Charm-SL antimicrobial inhibition tests. The Charm-AIM test kit screens for antimicrobial residues above MRLs allowed by the European Union for five common families of antimicrobials, while the Charm-SL test kit is used specifically to detect tetracyclines and β-lactam antibiotic residues that do not meet United States tolerance/safe levels. The limits and ADI levels prescribed by the Codex Alimentarious Commission (CAC) are presented in Table 1.

2. Materials and methods

2.1. Study areas and populations

Study sites were selected to provide contrasting types of markets in urban and rural locations and dairy production systems important in Kenya. For the consumer survey, the study was conducted in Nairobi and Nakuru urban areas and in rural areas adjacent to Nakuru town. For the market study, Nakuru and Narok districts were chosen to represent extensive production systems, low population density and medium market access, while Kiambu and Nairobi districts represented an intensive production system, high population density and high market access.

2.1.1. Consumers

Consumers were sampled within the three contrasting sites as follows: Nairobi city and Nakuru district (urban and rural) each have 120 census clusters. For each, 30 clusters were randomly selected. Within each selected cluster, seven households were randomly chosen for a total of 210 households. Each randomly selected household was visited, and milk samples obtained from those households consuming unpasteurized milk.

2.1.2. Market agents

The sampling of market agents varied by their location and type (Table 2). Divisions considered by key informants to have dairying as an important activity were selected in each of four targeted districts representing contrasting combinations of dairy production potential and market access. In Nairobi, market agents were sampled in 5 of 8 divisions, in Kiambu 5 of 5, and in Nakuru (urban and rural) 5 of 9. In addition, market agents in Narok, the chief town in Narok district, a predominately pastoralist area adjacent to Nakuru, were sampled. As for market agent types, all cooperative societies, cooperative

Table 1
Antimicrobial residue test detection ranges/levels for Charm AIM-96 and Charm-SL test kits, their maximum residue limits (MRLs) as set by the European Union and the United States, and acceptable daily intake (ADI) prescribed by the Codex Alimentarious Commission

Antimicrobial drug	Test detection range/level (μg/kg)		MRLs (μg/kg)		Codex ADI (μg/kg body weight)
	EU	US	EU	US	
Sulfamethazine	10–50	–	100[a]	–	50
Gentamicin	30–100	–	100	–	20
Tylosin	40	–	50	–	–
Tetracyclines					
Chlortetracycline	–	225–275	–	300	30
Oxytretacycline	150–300	125–175	100[b]	300	30
Tetracycline	–	50–70	–	300	30
β-lactams					
Cephaspirin	–	13.7	–	20	–
Cetiofur	–	46.0	–	50	50
Ampicillin	–	8.5	–	10	–
Amoxicillin	–	5.6	–	10	–
Penicillin G	3–4	3.6	4	5	30 μg/day

Sources: Adapted from Charm Sciences Inc., USA and Codex Alimentarious Commission Website.
[a] Total sulfa drugs.
[b] Total tetracycline drugs.

collection centers and self-help groups were sampled. Up to 30 milk/snack bars, milk shops and mobile traders were sampled in a selected division. For divisions with more than 30 milk traders, selection was stratified to cover all major markets in the division.

Both consumers and market agents were sampled in two different seasons and a 50 ml milk sample collected each time. An attempt was made to sample the same consumers and market agents in the second season. When this was not possible, an alternate was chosen. In addition, 110 pasteurized milk samples were randomly collected from supermarkets and kiosks (small roadside shops) in Nairobi and Nakuru.

2.2. Screening by the Charm AIM-96 test kit

All samples were screened using the Charm AIM-96 antimicrobial inhibition assay screening kit (Charm Sciences Inc., USA) according to the manufacturer's recommendations. The kit tests for unacceptable residue levels for drugs belonging to any of the following antimicrobial families: β-lactams, tetracyclines, aminoglycosides, macrolides and sulfonamides. Briefly, 50 μl of each sample was added in duplicate to the microtitre plate (96 flat bottomed wells) followed by 200 μl of a mixture of *B. stearothermophilus* spore tablet and lyophilized medium dissolved in 22 ml of deionised water. The plate was then sealed by special tape and the lid firmly secured by screws before incubation in the Charm AIM-96 incubator for 3–4 h. Positive and negative controls were also included in the assay. The positive control consisted of antibiotic free milk determined using *Micrococcus lutea* inhibition assay mixed with Penicillin G (4 ppb) or sulfamethazine (50 ppb) standard. The positive control mixture consisted of a 50 μl of drug free milk and 200 μl of bacterial spores and lyophilized media, while the negative control consisted of 50 μl of negative control tablet dissolved in distilled water and 200 μl of the test bacteria and media dissolved in deionised water. After incubation, test results were read using a reference colour contrast chart supplied by the manufacturer.

2.3. Tests using Charm-SL β-lactam and Charm-SL tetracycline kits

Positive milk samples screened by the Charm AIM-96 test kit were tested for β-lactam antibiotics and tetracycline using the Charm-SL rapid one step assay (ROSA) test kit (also from Charm Sciences Inc, USA) following the specified procedure. Briefly, for the β-lactam test, the supplied test strips were placed in the Charm-SL ROSA incubator and 300 μl of milk sample added to the sample compartment and sealed. The mixture was sealed, incubated for 4- (SL tetracycline) and 8- (SL β-lactam) min, and the test strips removed and read visually using a results chart and with the ROSA reader. Using similar test strips, each milk sample was also similarly tested for tetracycline residues after diluting the sample 1:2 using a buffer supplied by the manufacturer. Both assays were compared to respective positive controls consisting of 5 ppb of Penicillin G or 300 ppb of oxytetracycline standards.

2.4. Experimental confirmation and comparison of the Charm tests

To experimentally confirm the performance and compare the test results obtained by the Charm AIM-96 and Charm-SL tests under local conditions, milk samples

Table 2
Comparisons of antimicrobial residues above recommended maximum residue limits as determined by Charm AIM-96 test result by location and cadre of market agents in Kenya

Sample category and location	Number tested (*N*)	Number positive (*n*)	Prev. (%)	Prob. exact χ^2	Prob. $n = 0$ if prev. = 1%	Prob. $n = 0$ if prev. = 5%	Number tested (*N*)	Number positive (*n*)	Prev. (%)	Prob. exact χ^2	Prob. $n = 0$ if prev. = 1%	Prob. $n = 0$ if prev. = 5%
Date: Season	*1–2/99: Dry*						*9–10/99: Wet*					
Consumers in Nairobi City	45	5	11.1				53	0	0.0		NS	**
Consumers in Nakuru Town	51	4	7.8				56	0	0.0		NS	**
Consumers in Nakuru Rural	110	15	13.6				105	17	16.2			
Overall	206	24	11.7	NS			214	17	7.9	***		
Pasteurized milk	110	9	8.2									
Date: Season	*5–6/99: Wet*						*11/99–2/00: Dry*					
Market agents in Nairobi												
Milk-bars	42	2	4.8				36	4	11.1			
Milk shops/kiosks	27	1	3.7				26	3	11.5			
Mobile traders	14	0	0.0		NS	NS	12	1	8.3			
Overall	83	3	3.6	NS			74	8	10.8	NS		
Market agents in Kiambu												
Coop.	15	0	0.0		NS	***	14	1	7.1			
Coop. Coll. points	21	0	0.0		NS	***	2	0	0.0		NS	NS
Milk-bars	9	0	0.0		NS	NS	7	1	14.3			
Milk shops/kiosks	14	0	0.0		NS	NS	20	1	5.0			
Mobile traders	14	1	7.1				14	2	14.3			
Overall	73	1	1.4	NS			57	5	8.8	NS		
Market agents in Nakuru												
Coop.	6	0	0.0		NS	NS	2	0	0.0		NS	NS
Self help groups	2	0	0.0		NS	NS	3	0	0.0		NS	NS
Coop. Coll. points	0		–		NS	NS	3	0	0.0		NS	NS
Milk-bars	18	0	0.0		NS	NS	14	0	0.0		NS	NS
Milk shops/kiosks	13	0	0.0		NS	NS	12	0	0.0		NS	NS
Mobile traders	26	3	11.5				22	2	9.1			
Overall	65	3	4.6	NS			56	2	3.6	NS		
Market agents in Narok												
Milk-bars	10	2	20.0				8	0	0.0		NS	NS
Milk shops/kiosks	3	0	0.0		NS	NS	4	0	0.0		NS	NS
Overall	13	2	15.4	NS			13	0	0.0	NS	NS	NS
Overall total (all market agents)	234	9	3.8	NS			200	15	7.5	NS		

Key: NS = not significant at 5%; ** = significant at 5%; *** = significant at 1%.

were collected from eight lactating cows (belonging to the Veterinary Faculty Farm, University of Nairobi) following their intramammary or intramuscular injection with therapeutic doses for mastitis of either 10% oxytetracycline (Multiject®) or Penicillin G/streptomycin (Multimast®) formulations. The cows were allocated equally to each group (two per route of injection and type of therapy). One pre-treatment and five post-treatment milk samples were collected every 24 h for five days.

2.5. Estimation of risk of consuming milk with antimicrobial residues

Laboratory results and individual consumer and trader data were analysed using Intercooled Stata 6.0 (Strata Corporation 702 University Drive East College Station, TX). Descriptive comparisons of prevalence proportions of samples with above recommended MRLs, as determined by the Charm-AIM test kit, were done between locations of consumers and market agents for both wet and dry seasons. The Fisher's exact chi-square test was used to compare prevalence proportions for various cadres of market agents within and between locations. Where no samples with drug residues were detected, the probability of this being the case given the sample size was tested using the hypergeometric probability exact formula for a population prevalence proportion of drug residues of 1% and 5%. The estimated prevalence levels were used to estimate the risk of exposure to milk with antimicrobial residues.

3. Results

From consumer households, 206 and 214 unpasteurized milk samples were collected in the wet and dry seasons, respectively; and, from informal market agents, 234 and 200 unpasteurized milk samples were collected in the wet and dry seasons, respectively. In addition, 110 pasteurized milk samples were collected from various retail outlets during the dry season.

3.1. Prevalence estimates of residues above recommended thresholds

The proportion of samples with antimicrobial residues exceeding recommended MRLs as detected by the Charm-AIM test varied widely by season, location and type of market agent (Table 2). Samples from rural consumer households had a consistently higher proportion of samples with residues (over 10%) across both seasons compared to generally lower but wider variation in proportion of samples with residues from households in urban areas (range = 0–11.1%). The proportion of pasteurized and packaged milk samples with residues (8.2%) was within this range.

Besides the notable influence of location in milk samples from traders in Table 2, there was a trend of decreasing prevalence levels for the residues with increased bulking of milk as indicated by the higher proportion of positive samples from rural areas and small mobile traders (who commonly avoided bulking to reduce risk of spoilage and in order to be able to identify the source) compared to bigger traders and bulking agents such as cooperatives. There were no significant differences between proportions of samples of market agents with residues between seasons and within locations. Surprisingly to us, none of the milk samples collected from the field that were positive on the Charm-AIM test was positive on the Charm-ROSA test as well. This necessitated the experimental confirmation and comparison of the two tests, the results of which are reported below.

The precision of the prevalence levels can be made given the sample sizes. Assuming overall individual sample prevalence estimates of approximately 8%, the overall sample of 212 milk samples per season would yield a 95% confidence limit ranging from 6.2% to 9.8%. Where no samples with drug residues were detected, the probability of a zero prevalence given the size of individual sample categories indicates the sample sizes were too small to distinguish between a population with prevalence of 5% from a population with no drug residues in most of these cases (Table 2).

3.2. Experimental confirmation and comparison of the Charm-AIM and -SL tests

Agreement between the two tests was good up to 72 h post-drug administration beyond which the number of Charm-SL test positive samples dropped sharply (Table 3). Both the milk samples that tested positive on the Charm-SL test at 96 h were from cows injected with β-lactam antibiotics (one intramuscularly and the other intramammary). The route of drug administration did not have an effect on the rate of disappearance of the residues in milk. These detectable limits were consistent with the limits established by the manufacturer of the two tests.

3.3. Risk of exposure to antimicrobial residues as determined by the Charm-AIM test

The highest prevalence level of 16% of marketed milk samples with unacceptable concentration of antimicrobial residues detected in rural locations indicates that, on average, the consumers could be exposed to such levels every sixth time marketed milk is consumed. If the milk is consumed daily, as many Kenyans do, the risk of exposure to milk with drug residues could be as high as

Table 3
Number of milk samples testing positive on Charm-AIM and Charm-SL tests following treatment of eight cows with therapeutic doses of oxytetracycline (10%) and Penicillin G formulations

Hours post-drug administration	0	24	48	72	96	120
Number testing positive on Charm-AIM test	0	8	7	7	7	7
Number testing positive on Charm-SL ROSA test	0	8	8	7	2	1

five times every month. At such a high frequency of intake, the probability of surpassing the ADI for the various drugs can be considerably high, depending on the concentration of the residues, which this study did not quantify. The highest risk of ingesting residues above the ADI levels prescribed by the Codex Alimentarious Commission was deemed to be for penicillin G-type or β-lactam antibiotics due to its low ADI of only 30 μg/day and the high frequency of usage of the antibiotic locally.

4. Discussion

The higher proportions of milk samples with residues from sources with minimal bulking such as rural households and small traders may indicate that dilution has some effect on the Charm-AIM test outcomes. The most likely source of abuse is likely to be non-observance of withdrawal periods after treatment of cows with antibiotics at farm level (Marteniuk, Ahl, & Bartlett, 1988; Rybinska et al., 1995). This source of abuse became more likely following liberalization of delivery of veterinary clinical services in Kenya and the subsequent entry into the market of many unauthorized animal health service providers. For example, a recent study estimated that about two-thirds of outlets for veterinary drugs are without authorized personnel who do not qualify for trading licenses to dispense veterinary drugs (Kuria, Nginyi, & Nganga, 2002). Addition of the antimicrobial agents to preserve milk along the market chain cannot also be ruled out though no respondent admitted to this practice.

Up to now, available reports of the negative effects of antimicrobial abuse attribute the problem to misuse of human drugs. The impacts, including costs to a community, of exposure to antimicrobial residues over long periods have not been documented. One of those costs is likely to be that a greater proportion of patients that could have easily responded to treatment with cheaper drugs become resistant to those drugs, necessitating the use of more expensive medicines.

The high prevalence levels of antibiotic and antibacterial residues indicate a need to begin to tackle the problem both at the farm and market levels. The initial critical control point for risk management should be to raise awareness amongst policy makers and to conduct further investigations at the farm level to define causal relationships to complement this data, and as a basis for designing targeted extension materials. Such targeted extension materials and effective penalties for non-compliance have been reported to be useful in solving the problem in many countries (e.g., Bester & Lombard, 1979).

The duration for which the Charm-AIM test detected drug residues in milk following experimental injection with therapeutic doses of oxytetracycline and Penicillin G is consistent with findings by Anderson, Moats, Rushing, Wesen, and Papich (1996) and results obtained using the high performance liquid chromatography (HPLC) method (Anderson et al., 1996; Dinsmore, Stevens, Cattell, Salman, & Sundlof, 1996). The low agreement between the Charm-AIM and Charm-SL tests after 72 h post-experimental drug injection may partly explain the differences observed in test results on field samples.

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