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Review

CONTEMPORARY ASPECTS IN CONTROL OVER RESISTANT TO ANTIBIOTICS MICROBIAL CONTAMINANTS OF FOOD, TAKING INTO ACCOUNT PECULIARITIES OF RELATED HEALTH RISK ASSESSMENT. PART 1

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Antimicrobials are widely used in agriculture to prevent and treat diseases and to stimulate growth of food-producing animals. However, this induces developing antimicrobial resistance among animal bacteria, and this resistance is then transmitted along food chains and spreads in the environment. It is commonly accepted at the moment that effective measures should be taken to contain it in food production, to prevent it from spreading on the global scale and to minimize related negative health outcomes. This can be achieved, among other things, due to intensifying inter-branch interactions.

This review aimed to consider contemporary aspects in preventing development of antimicrobial resistance in microorganisms that contaminate raw materials and processed food products; to dwell on how the issue is controlled in food production both in Russia and abroad; to focus on trends and prospects of developing new effective measures in the sphere.

The review involved analyzing domestic and foreign regulatory and legal documents concerning prevention of antimicrobial resistance and analysis of related risks; generalizing and analyzing latest scientific research works published in reference databases including Web of Science, Scopus, PubMed, Google scholar.

As a result, we described the experience accumulated in organizing monitoring over prevalence of antimicrobial resistance in foreign countries, to generalize international recommendations as well as regional and national ones on monitoring over microorganisms that are resistant to antimicrobials, and to highlight practical activities aimed at preventing occurrence and spread of antimicrobial resistance in food production. We substantiated certain peculiarities of related health risk assessment, namely, occurrence of genetic determinants of antimicrobial resistance and antibiotic residues in food together with resistant microorganisms. We also formulated basic principles of organizing and conducting monitoring over antimicrobial resistance in food chains (with the focus on antimicrobial medications that are crucially important in medicine). These principles can be applied in the Russian Federation within programs aimed at preventing antimicrobial resistance.

Key words: *antimicrobial resistance, antimicrobial veterinary medications, monitoring over antimicrobial resistance, sub-inhibitory doses of antimicrobials, food safety, harmful factors related to antimicrobial resistance, markers of antimicrobial resistance in food, antibiotic residues, genes of antimicrobial resistance in food isolates, food isolates with antimicrobial resistance.*

Annually approximately 500,000 people die due to antimicrobial resistance all over the world [1].

Multiple efforts have been made recently, both at the international and local level, to prevent zoonotic agents from becoming resistant as a response to antimicrobial use in veterinary; a lot is done to prevent incidence among population caused by this resistance. The Global Action plan on antimicrobial resistance

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which was approved on the 68th WHO General Assembly introduced "One Health" inter-brunch approach. This approach involves implementing complex activities aimed at fighting the phenomenon both in healthcare and agriculture. There are several directions within it including monitoring over resistance of circulating agents, prevention of infections, rational antimicrobial use and implementation of alternatives to antimicrobials, etc. The WHO and FAO approved on several policy documents for supporting actions taken in different countries in agriculture, including the Guidelines on use of medically important antimicrobials in food-producing animals and the FAO Action plan on antimicrobial resistance 2016–2020 [2, 3].

In 2017 the Strategy for preventing spread of antimicrobial resistance for the period up to 2030 was adopted in the Russian Federation. The document fixes the necessity to examine prevalence of antimicrobial resistance, develop relevant legislation in due time and implement activities aimed at containing it in food production[1]. At the same time Rospotrebnadzor and FAO started a joint project aimed at assisting their partner states in the Eastern Europe and Central Asia in developing national strategies and action plans on fighting against antimicrobial resistance[2]. The primary tasks of the project are to enhance a country potential regarding monitoring over pathogen resistance and to organize systems for laboratory control over this resistance regarding food products with the major project reference center to be located in Russia.

All the aforementioned strategies are undoubtedly justified, first of all, with respect to food products being the primary object under surveillance since basic quantities of environmental contaminants (up to 70 %) enter the body with food and resistance is known to be the most important attribute of microbial contaminants. Control over it in various pathogens is vital since it is necessary to minimize abovementioned outcomes of foodborne toxicoinfections (FBTIs) and to search for effective therapy.

However, we should point out that fighting against antimicrobial resistance in foodborne bacteria is primarily aimed at preventing its occurrence and spread along food chains as well as its transmission to gut microbiota [2, 3]. Monitoring which is limited to pathogens (in most countries they are predominantly Salmonella in raw foods) can't give a clear picture of the examined phenomenon even if it is well-organized and efficient. Population exposure to non-pathogenic potential resistance transmitters in cooked foods is much higher than that covered by such monitoring and therefore should be estimated as per relevant indicators.

This example provides clear evidence that certain weak spots can be detected already at an initial stage in developing and implementing activities aimed at fighting antimicrobial resistance. Accordingly, it is necessary to constantly apply logical thinking to understand the problem better, to adjust measures and to harmonize them with the best available practices if we want to enhance surveillance over antimicrobial resistance in every country all over the world.

Aim. This review aimed to consider contemporary aspects in containing and controlling antimicrobial resistance in microbial contaminants in food as well as trends and prospects of developing effective measures in the sphere.

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[1] Strategiya preduprezhdeniya rasprostraneniya antimikrobnoi rezistentnosti v Rossiiskoi Federatsii na period do 2030 goda: utv. rasporyazheniem Pravitel'stva Rossiiskoi Federatsii ot 25.09.2017 № 2045-r [The Strategy for preventing spread of antimicrobial resistance in the Russian federation for the period up to 2030: approved by the RF Government Order on September 25, 2017 No. 2045-r]. *GARANT: the information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/71677266/ (November 29, 2021) (in Russian).

[2] O realizatsii rasporyazheniya Pravitel'stva Rossiiskoi Federatsii ot 03.02.2017 № 185-r: Prikaz Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka ot 26.02.2018 № 97 [On implementation of the RF Government Order dated February 03, 2017 No. 185-r: The Order by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing issued on February 26, 2018 No. 97]. *KODEKS*. Available at: http://docs.cntd.ru/document/551223268 (November 29, 2021) (in Russian).

Materials and methods. The review involved analyzing domestic and foreign regulatory and legal documents specifying how to contain antimicrobial resistance and analyze related risks. We generalized and analyzed latest scientific research works published in 2005–2021 in reference databases including Web of Science, Scopus, PubMed, and Google scholar. We searched for literature sources using the following key words: antimicrobial resistance, food isolates resistant to antimicrobials, antimicrobials in forage, veterinary antimicrobials, monitoring over antimicrobial resistance, horizontal transfer of antimicrobial resistance genes, sub-inhibitory doses of antimicrobials.

To organize an activity: what is necessary for its effectiveness? The first step in implementing activities against antimicrobial resistance in any country is to develop and adopt a national action plan. The RF Government approved a middle-term action plan for 2019–2024 within the Strategy for preventing spread of antimicrobial resistance for the period up to 2030[3]. Given specific tasks on fighting against resistance in food chains, two sets of measures were included into the plan; they were aimed at preventing both its occurrence and spread. The first set is aimed at developing a regulatory base in the short-term (prohibiting use of veterinary antimicrobials with non-therapeutic purposes or use of medications not included in sanctioned lists as well as stricter regulation of such substances in forage production). Non-therapeutic use means that healthy animals are fed with forages which contain antimicrobials in low doses; though, it is still permitted to apply antimicrobial prevention in intensive animal farming when there is a danger of a mass infection among cattle and poultry.

The second set is aimed at preventing and containing circulation of infectious agents which have antimicrobial resistance. The key component here is organizing and conducting monitoring over antibiotic residues in food raw materials and food products and resistance of bacteria isolated from animals, raw materials and food products; this monitoring can also be conducted within international cooperation. According to the plan, a unified interdepartmental database is to be created with participation by the RF Public Healthcare Ministry, Rospotrebnadzor, and other concerned federal executive authorities. This database will contain data on prevalence of antimicrobial resistance. Other important steps are to optimize and standardize methods applied to monitor microbial resistance. These tasks are being tackled at the moment and there are two active platforms: AMRmap[4] in medicine and AMRCloud[5] in veterinary medicine.

In 2021 the plan envisaged creating a list of veterinary antimicrobials with limitations on their use including in food-producing animals. We should note that similar lists created by the WHO and EU contain, for example, chloramphenicol, nitrofuranes, and metronidazole[6] [4], whereas these important provisions have been approved on in the RF for the first time only recently and after a long-term discussion.

At the same time there are very few concrete data in the plan on interdepartmental interactions in RF regions and terms are not specified (2019–2024). This will require certain adjustments to provide implementation of actual activities.

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[3] Ob utverzhdenii plana meropriyatii na 2019–2024 gg. po realizatsii Strategii preduprezhdeniya rasprostraneniya antimikrobnoi rezistentnosti v RF na period do 2030 g.: rasporyazhenie Pravitel'stva RF ot 30.03.2019 № 604-r [On Approval of the action plan for the period 2019–2024 on implementing the Strategy for preventing spread of antimicrobial resistance in the Russian Federation for the period up to 2030 dated March 30, 2019 No. 604-r]. *The RF Government*. Available at: http://government.ru/docs/36320/ (November 29, 2021) (in Russian).

[4] AMRmap: online platform for analyzing data on antimicrobial resistance in Russia. Available at: https://amrmap.net/ (November 24, 2021).

[5] AMRcloud: web platform for analysis and sharing of AMR surveillance data. Available at: https://amrcloud.net/en/ (November 29, 2021).

[6] Reglament Evropeiskoi Komissii 37/2010 ot 22.12.2009 o farmakologicheski aktivnykh veshchestvakh i ikh klassifikatsii v otnoshenii maksimal'no dopustimykh ostatkov v pishchevykh produktakh zhivotnogo proiskhozhdeniya [Commission Regulation (EU) No. 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin]. Saratov, IPR media, 2019, 144 p. (in Russian).

As the action plan was being discussed and approved by the RF Federal Assembly, the senators adopted several legislative initiatives for the highest federal executive authorities. Thus, the RF Public Healthcare Ministry was given a task to create a federal system for monitoring over resistance of the leading infectious agents causing human infections. The system is to be created on the basis of a network comprising local centers (laboratories at medical and prevention organizations) in RF regions with its methodical verification center located in Smolensk Medical University. The Ministry will also be responsible for providing finance and material and technical support for these centers. This initiative fixes and enhances the potential of the former federal scientific and methodical center for monitoring over antimicrobial resistance which was previously created by the Ministry in 2015 and provides the logistics for the national database on antibiotic resistance and control over it in clinical medicine[7,8].

However, no similar decisions have been made with respect to monitoring over non-clinical strains, first of all, foodborne ones. The federal executive authorities who are responsible for the sphere are to develop a proper scientific-methodical and regulatory base. Thus, Rospotrebnadzor should develop relevant clinical recommendations and harmonize them with the existing clinical recommendations on determining antimicrobial sensitivity of bacteria isolated from food products and food raw materials. These recommendations should be based on using epidemiological boundary values of strain sensitivity estimation. The RF Agricultural Ministry is to develop unified veterinary rules for use of veterinary antimicrobials in animal farming[7].

We remember that all the aforementioned documents are significant; still, their development is only a step in a whole set of activities aimed at creating a necessary system in the country for control over antimicrobial resistance which is transmitted with food. In all developed countries such transmission is given the same attention as clinical one due to objectively higher volumes of antimicrobials used in contemporary food production. Thus, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) provides data on how antibiotics are distributed in the world and thereby indicates that ratio of hospital purchases and chemists' sales to purchases by manufacturers using antibiotics in food-producing animals and plants is 20 % : 80 %. When recalculated per 1 kg of a standardized body mass of an ultimate consumer, 1.5 times higher volumes of such medications are sold to be used in animal farming than in treating people [5].

Therefore, given the selective exposure to antibacterial medications from all possible sources, occurring resistance determinants unavoidably penetrate the environment and are involved into the joint circulation (Figure) [6].

This situation calls for counteractions in two directions, by imposing limits on use of antimicrobials and making it rational in all possible spheres and by breaking paths of resistance spreading in the environment, including food chains as the objects being the most susceptible to contamination. The most effective way is to combine efforts by all concerned parties, to create a common database on preparations applied in medicine and veterinary medicine and on resistant isolates, and to coordinate all the activities from a common center.

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[7] Antibiotikorezistentnost' v Rossii: rasprostranennost' i zakonodatel'nye initsiativy v reshenii problem: reshenie zasedaniya Ekspertnogo soveta po zdravookhraneniyu Komiteta SF po sotsial'noi politike ot 03.07.2018 № 3.8-13/1616 [Antibiotic resistance in Russia: prevalence and legislative initiatives on finding solutions to the related issues: the decision made at the meeting by the Expert Council on Public Healthcare of the Federal Assembly Committee on social policy dated July 3, 2018 No. 3.8-13/1616]. *The National Association of experts on infection control*. Available at: http://nasci.ru/?id=4261 (November 29, 2021) (in Russian).

[8] O federal'nom nauchno-metodicheskom tsentre monitoringa rezistentnosti k antimikrobnym preparatam: Prikaz Minzdrava Rossii ot 03.06.2015 № 302 [On the federal scientific-methodical center for monitoring over antimicrobial resistance: the Order by the RF Public Healthcare Ministry issued on June 03, 2015 No. 302]. *KODEKS*. Available at: https://docs.cntd.ru/document/420281390 (November 29, 2021) (in Russian).

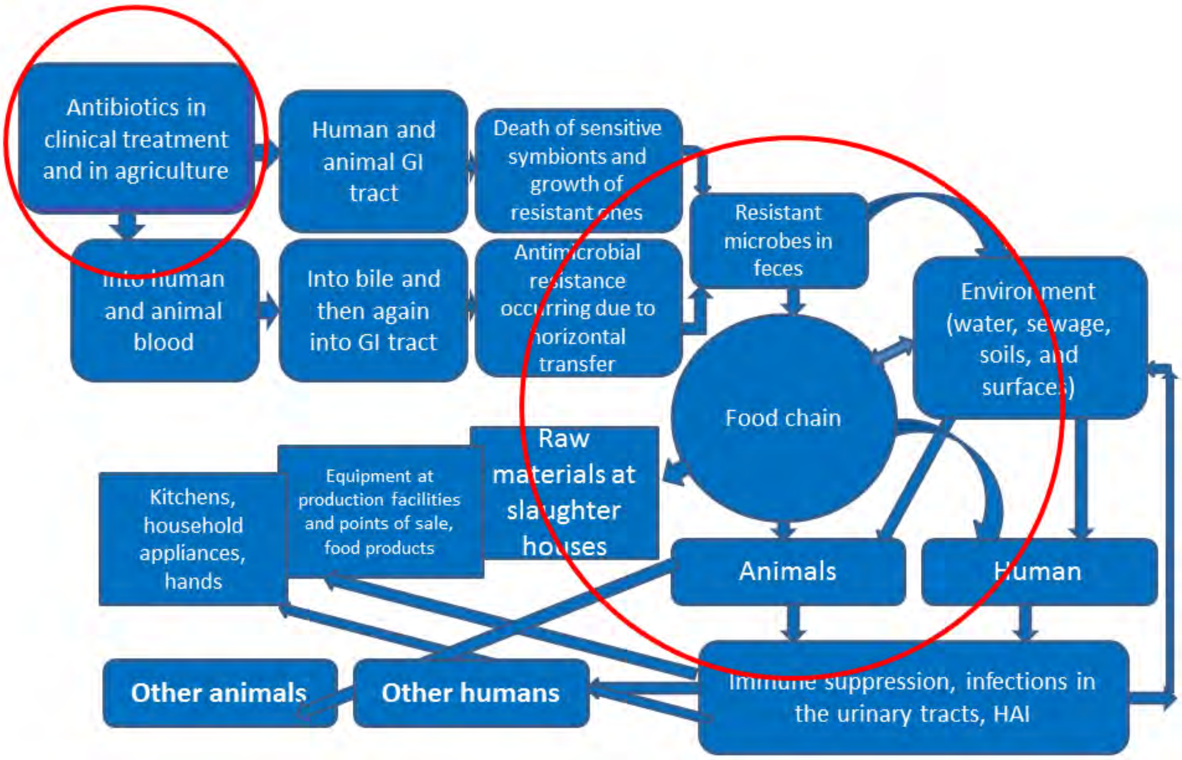

Figure. Circulation of resistance determinants in the environment

In our country, there are monitoring activities regarding antimicrobial resistance in bacteria circulating in various environmental objects, including the food chain, but this monitoring cannot yet be considered systematized.

Laboratory services existing at medical organizations deal with strains which spread from sick people and objects in in-patient hospitals but their target microbes are those which cause suppurative infections or so called Healthcare-Associated Infections (HAIs) and they don't usually pay any attention to agents causing FBTIs. And we should remember that nosocomial enteric bacteria acquire the highest resistance to semi-synthetic penincillins and 3rd – 4th generation cephalosporins (from 75 to 98 % strains), as well as to 3rd generation fluoroquinolones (70 %) [7].

Regional veterinary laboratories analyze microorganisms isolated from sick and dead animals at animal farms. According to data provided by Rossel'khoznadzor (the Federal Service for Veterinary and Phytosanitary Surveillance) in 2012 50–90 % of *E. coli*, *Salmonella*, *Enterococcus spp.* were highly resistant to tetracyclines, chloramphenicol, furazolidone; there was also growing resistance of *Salmonella spp.* to ampicillin, doxycillin, streptomycin, ciprofloxacin and norfloxacin in comparison with 2009.

Isolates of nontyphoidal salmonella from people and environmental objects, including food, are examined in Rospotrebnadzor's national reference center. In 2017 isolates turned out to be resistant in 58.5 % cases overall, including 93 % cases among *S. infantis*; *S. typhimurium*, 69 %; *S. enteritidis*, 47.5 %. 4 % of strains were resistant to 10 and more medications. Predominantly, isolates were resistant to cefurotoxime (44 %), cefalotin (29 %), ticarcillin (16 %), amoxicillin (15.5 %), piperacillin and tucarcillin / clavulanic acid (15 % each), cefotaxime (12 %) and co-trimaxozole (11 %)[9].

[9] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2017 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2017: The State Report]. *Rospotrebnadzor*, 2018, 268 p. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=10145 (November 29, 2021) (in Russian).

Since 2018 monitoring over antibiotic residue and resistance of bacteria isolated from food raw materials and food products has been conducted by a reference center organized within the above-mentioned international project at Rospotrebnadzor's Central Scientific Research Institute for Epidemiology[2]. By the beginning of 2019, experts created profiles of 1068 pathogenic strains (*Salmonella spp.*, *S. aureus*, *L. monocytogenes*) isolated from food samples which were selected in 7 different food product groups with elevated total microbial contamination [8]. 42.7 %, 38.7 % and 18.6 % strains accordingly turned out to be resistant.

Non-pathogenic food isolates are not monitored in the RF. There are data in scientific publications that coliform bacteria and enterococci occurring in qualitative domestic milk and meat products have some resistance to antimicrobials which varies from 10 to 90 %. Enterococci resistant to ciprofloxacin are detected in 80–90 % cases. *Klebsiella* and *E. coli* with multi-resistance (up to 8 antibiotics) are detected in 17.4 % cases [9, 10]. Campylobacteria in poultry meat are practically totally resistant to 3rd generation fluoroquinolones (96 %), highly resistant to tetracyclines (88 %) and semi-synthetic penicillins (57 %) [11].

Obviously, in the RF resistant strains prevail not only in clinical environment but also in food chains and antimicrobial resistance is detected for clinically important antimicrobials of the latest generations. But even if we have this latest data, we still can't get a clear picture of resistance as a whole and any effects produced by the introduced measures. The reason is that, apart from separate monitoring activities in different spheres, there is no common functional network comprising local centers for control over non-clinical isolates. There aren't any decisions either on how to provide such centers with financial and logistic support.

So, we generalized international recommendations and experience accumulated by regional and national systems for monitoring over antimicrobial resistance [3, 12, 13]. As a result, we were able to formulate optimal principles for monitoring over it in food chains at the national level:

- aim: to protect human and animal health by managing risks and minimizing resistance in zoonotic agents, commensal and technological microorganisms as well as by selecting effective therapies;
- interdepartmental interactions and coordination by a national reference center(s);
- taking samples of strains alongside the whole food chain: healthy and sick animals, forages, food raw materials and food products, sick people (consumers);
- standardized sampling protocols;
- sampling design and criteria which conform to validity requirements;
- target strains: pathogenic bacteria which cause food-borne infections, non-pathogenic microorganisms (gut microbiota, biotechnological microorganisms);
- strain identification down to genus / species;
- determining phenotypic sensitivity of strains to antimicrobials using standardized techniques;
- systemic control over research quality;
- use of common and harmonized assessment criteria (boundary values) for minimal inhibitory concentrations (MIC) and zones where a growth in quantities of "epidemiological" bacteria could be slowed down;
- identifying determinants, nature and mechanisms of antimicrobial resistance using reproducible analysis techniques, including molecular and genetic ones;
- storage of original strains in cryobanks for further studies focusing on resistance mechanisms;
- participant confidentiality, transparent and well-mapped results, effective partnership, and validated approaches.

Practices applied in well-organized monitoring systems in different countries highlight the significance of simultaneous surveillance over a range and quantities of antimicrobials used both in people and animals. This is done by collecting data on sales on the national level, observations over use of medications at hospitals and animal farms as well as by direct control over their residues in forages and manufactured products [5, 13].

When a system is integrated in such a way, it fully corresponds to tasks set within "One Health" approach. Comparing data on resistance which come from different sources provides competent authorities with a whole number of opportunities to assess and manage risks at the national level. Among other things, this allows making correlations between data on antimicrobial use and resistance in different socioeconomic sectors, identifying emerging risks of antimicrobial resistance, prioritizing these risks along food chains (which sector? which bacteria? what resistance? which products?) and creating an authentic database for developing specific policies and effective measures.

The European antimicrobial resistance monitoring for zoonotic and indicator bacteria of animal, human, and food origin that started in 2005 is in line with most aforementioned principles. In 2017 a new action plan was adopted with its focus on fighting this resistance and its basic motto being "turning the EU into a region with best applied practices". The Action plan includes more than 75 specific tasks. The focus is on intensified research, development, and innovations, finding new solutions and instruments to prevent and treat infections as well as better diagnostics of resistance prevalence. A whole section is devoted to intensifying efforts on developing global measures and reducing risks related to resistance all over the world.

In 2019 the UN Secretary-General Antonio Gutterres made a statement stressing out that integration was crucially important in fighting against antimicrobial resistance. The statement was made on the 73rd session of the UN General Assembly summarizing all the efforts on implementing national action plans and measures taken to implement the political declarations made on the high-level meeting in 2015. It was said that "Along with the human health sector, the full engagement of the animal and plant health and environmental sectors through a "One Health" approach and a functional multisectoral coordination mechanism are urgently needed in each country; national action plans should be reviewed to reflect a comprehensive "One Health" approach" [14].

To sum up all these data, we can conclude that it is urgent to implement integral assessment of microbial resistance in Russia, not only in the clinical sphere but also in food production. To do that, legislative initiatives are required immediately; they should provide support for inter-brunch interactions by creating an interdepartmental structure with a coordination scientific-methodical center and a network comprising local monitoring centers.

Risk-based approach in global fighting against resistance in food production and distribution. In 2018 the second intergovernmental target group was created by Codex Alimentarius Commission as a response to growing attention paid to threats for public health imposed by antimicrobial resistance. Its major task was to develop science-based guidelines on coordinated management of antimicrobial resistance along the whole food chains [15]. The RF participates in both parts of this project which concentrate on revising the Code of practice to minimize and contain antimicrobial resistance in food products (CAC/RCP 61-2005) and developing the Guidelines on integrated monitoring and surveillance over food-borne antimicrobial resistance.

CAC/RCP 61-2005 is being actively revised by remote work teams with 41 EU countries and regions participating in the process. The document should provide grounds for developing measures aimed at reducing risks of resistance transmission with food. These measures can be implemented by any country within its national strategies on antimicrobial resistance taking its priority and capabilities into account and during a reasonable period of time. At present, 3 stages out of total 8 planned to be considered have been completed [16].

This code of practice is an integral part of risk analysis regarding foodborne antimicrobial resistance; it focuses on managing risks. All instructions on relevant measures and practices along food chains included into it are based on risk assessment and analysis [17]. These instructions cover such areas as responsible and reasonable production, registration, sale, deliveries, prescription, and use of antimicrobials in animal farming, aquaculture, plant growing as well as forages. They also provide guidance on how to contain development and spread of resistant microorganisms, and how to identify resistance determinants in food processing, cooking, storage, transportation, selling, and consumption. The Code is interrelated with the Guidelines for risk analysis of food-borne microbial resistance (CAC/GL 77-2011) created in 2011 with its aim being to develop all components in analyzing risks of foodborne antimicrobial resistance, including science-based health risk assessment methodologies.

Peculiarities in assessing risks of foodborne antimicrobial resistance. CAC/GL 77-2011 describe how to assess health risks caused by presence of antimicrobial resistant microorganisms (AMRM), their determinants (AMRD) and/or residues of antimicrobial use (AMU) to which resistance is expressed in food products and animal forages and their transmission along food chains [17]. In Russia a similar guide covering these issues was introduced in 2012 and entitled MR 2.1.10.0067-12 "Assessment of health risks caused by exposure to microbial factors in food products" [10].

Negative outcomes for human health caused by resistant food isolates are not always urgent and can be even rather latent (in case of genetic determinants). Therefore it is more difficult to assess them than to assess risks related to clinical resistance or risks related to microbial contamination in food products. Such outcomes should be separated from all other obvious ones caused by microbial factors and assessment methodology in their case should be based on specific approaches.

In general, assessment of risks caused by resistance transmitted with food is not structurally different from the conventional microbial risk assessment (MRA) [18]. Initially a risk profile is created as a combination of a specific product with AMRM, AMRD or AMU. However, we should bear in mind much more information sources than it is stipulated by MRI for infectious agents which cause FBTIs. Usual information sources include monitoring programs, epidemiological analyses of outbreaks and sporadic cases caused by resistant microbes, clinical examinations and reports on incidence of foodborne infections, results produced by antimicrobial therapy and a correlation between resistance and frequency and severity of related diseases. But apart from that, we should take into consideration national or regional recommendations on FBTIs treatment, enhanced data on microbial properties (pathogenicity, virulence, survivability and growth in food products and the environment, resistance to selection and gene element transfer (in vitro, in vivo)) and resistance determinants (mechanisms, localization, cross resistance to other antimicrobials transmission between microbes and spread in the environment). It is important to have an insight into relations between resistance, virulence, and adaptability; to understand AMU pharmacokinetics and pharmacodynamics when such medications are used to treat humans and animals; to examine correlations between antimicrobial use and resistance of flora in animals and agricultural plants. It is also necessary to analyze data on food products bearing in mind their influence on risk management (how they are treated and processed prior to consumption, pH, A_w etc.), to describe factors and risks influencing how safe a given food product is on its way to ultimate consumers (primary production → processing → storage → processing → distribution → consumption)[10] [17].

Assessment of risks caused by foodborne resistance, just as in case with MRA, involves hazard identification, exposure estimation, hazard characteristics, and risk characteristics. But given all specificity of the issue, each stage unavoidably involves epidemiological monitoring which is not a traditional component in MRA[10]. This monitoring conducted at each stage in assessment allows spotting out a correlation with consumption of food which is not simply contaminated with pathogens or antibiotic residues but with consumption of food which contains such a harmful factor as

[10] MR 2.1.10.0067-12. Otsenka riska zdorov'yu naseleniya pri vozdeistvii faktorov mikrobnoi prirody, soderzhashchikhsya v pishchevykh produktakh. Metodicheskie osnovy, printsipy i kriterii otsenki: metodicheskie rekomendatsii [MR 2.1.10.0067-12. Assessment of health risks caused by exposure to microbial factors in food products. Methodical grounds, assessment principles and criteria: methodical guidelines]. Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 44 p. (in Russian).

antimicrobial resistance. Among other things, such assessments include additional steps which can't be found within simple MRA:

– hazard identification, apart from describing resistance of microbes and/or determinants in forages, aquaculture, or food matrices, involves examining the same features of sensitive strains belonging to the same or related taxa and/or them having determinants;

– exposure estimation involves calculating frequency and quantity of resistant microbes and/or determinants which result from AMU in all possible ranges, from food-producing animals to agricultural plants (from animal wastes) and in finished food products ready to be consumed after processing. And when resistance determinants are target hazards, including those in commensal bacteria, then it is advisable to consider rates of their transmission to human pathogens and symbionts which become resistant. Synthesis of data on frequency and quantities of target agents in food taking into account all factors which can influence these indicators and knowledge about structure of consumption determine exposure to AMRM, AMRD or AMU for a person, a group, or population as a whole.

– hazard characteristics involve estimating contagion probability, a number of disease cases and other outcomes as a response to exposure; the stage also involves identifying additional health outcomes (more frequent and severe pathologies, their longer duration, frequency of infections in blood flow, admissions to hospitals and mortality, failed treatments) caused by antimicrobial resistance. Similar to the 1st stage in MRA, reactions by sensitive microorganisms are also estimated;

– risk characteristics combines all conclusions made at the previous stages; it can be given using such indicators as an individual risk of a disease due to resistance in food, population health risk (risk for specific subgroups), risk caused by a single meal or annual consumption, or as calculated damage due to diseases. Validity of the ultimate estimation depends on changeability, uncertainty and assumptions accepted during MRA.

Ultimate assessment results are taken into account in giving grounds for systemic measures aimed at preventing diseases among population, implementing new technologies in agriculture, and making choices on new prospective research directions in science.

Another specific feature is the necessity to permanently reevaluate risks due to frequent changes in AMU range applied in agriculture or to new detected mechanisms of resistance[10].

Development of the risk-based approach within an integrated system for monitoring and surveillance. Although we are provided with the legitimate risk analysis methodology described in CAC/GL 77-2011, there still haven't been any etalon risk assessments performed either at national or global levels. Ideally, integrated systems for monitoring and surveillance which are outlined in the WHO-AGISAR guidelines should be developed taking into consideration all possible health risks related to foodborne antimicrobial resistance. Among other things, they should provide a solid basis for assessing population exposure to resistant microbes and/or determinants [5]. But such knowledge has turned out to be almost unavailable in most countries. This is primarily due to a very vague idea about scales in which preparations are used in agriculture and we should remember that scopes of occurring antimicrobial resistance depend on them. Another reason is that resistance profiles in people vary greatly depending on selected microorganisms and geographical regions [15]. This is confirmed by the fact that the overall global market of goods for animal health is estimated to be equal to 22 billion USD (in 2011) but only 22 % of all UN member countries have a full-fledged and operational system for collecting data on use of antimicrobials in animal farming. At present there is no any common database with data on global use of antimicrobials in farm animals [15].

To solve the aforementioned issues, experts have proposed draft Guidelines on Integral Monitoring and Surveillance (GLIS) of Foodborne Antimicrobial Resistance. The document conforms to the concept stated by the WHO-AGISAR but also envisages step-by-step implementation taking into account priorities, infrastructure, capabilities and resources in different countries [19]. The draft describes a procedure for coordinated systemic data collection and sampling at all stages in food chains, their testing to determine AMRM, AMRD or AMU in them using harmonized methods for sampling, investigation, and reporting as well as complex analysis of relevant epidemiological data on humans, animals, food products, agricultural plants, and environments at food production.

All this indicates that GLIS data on AMRM, AMRD and AMU in food chains, including their transmission during food processing and spread in the environment, are not only useful for solving issues related to food safety but also provide important information for risk assessment and making decisions on managing risks caused by antimicrobial resistance for humans, animals, and plants. That is, these data are an integral, well-organized, and well-structured part of theoretical and practical risk assessment and a very important stage in risk analysis.

In this context a major issue in any country, Russia included, is how to provide proper management and coordination within GLIS systems and to support its legitimacy with political decisions made by the highest executive authorities and with a relevant legal and regulatory base. The Action plan on implementation of the Strategy for preventing spread of antimicrobial resistance in the Russian Federation for the period up to 2030[3] stipulated the responsibility borne by the RF Public Healthcare Ministry, Rospotrebnadzor, and other concerned federal executive authorities for developing relevant departmental documents in 2020[3]. These documents should cover such issues as organizing and conducting monitoring over antibiotic residues in food raw materials and food products and over antimicrobial resistance in bacteria isolated from animals, food raw materials and food products. Another important issue was to create and develop a common (interdepartmental) database on prevalence of antimicrobial resistance and to include this database into a state information system for providing chemical and biological safety which is being created at the moment. However, it is rather complicated to achieve relevant coordination in the process since public healthcare organizations and concerned federal executive authorities still participate in it independently from each other. It is also difficult to coordinate implementation of separate systems for monitoring over antimicrobials turnover (monitoring over turnover of preparations used in medicine and monitoring conducted by the federal state information system in veterinary medicine). Both points require certain adjustment and well-grounded initiatives, especially with respect to assigning a relevant authority responsible for their implementation.

But still, in 2018 monitoring over antibiotic residues in food raw materials and food products and antimicrobial resistance in food isolates was introduced within the aforementioned international project by Rospotrebnadzor and FAO[2]. This monitoring is well in line with all the concepts outlined in the new Guidelines. Full-fledged GLIS can be implemented on its basis; to do that, it is necessary to introduce the same monitoring process in other spheres in food chains including veterinary medicine, environments at production facilities, and consumers' health. The process will require certain adjustments made in the regulatory and legal documents.

Aspects of the risk-based approach in selecting GLIS directions and objects. This new progressive approach should be implemented as a risk-based one at each stage in conformity with CAC/RCP 61-2005 [16] and MR 2.1.10.0067-12[10] and take into account all available knowledge on risks related to foodborne resistance and accumulated international experience. It is also important to provide data compatibility at the global level.

At initial stage in monitoring a correct choice should be made on GLIS objects (AMRM, AMRD and AMU to which resistance in expressed in food chains). To do that, it is vital to analyze relevant legitimate data on types and quantities of antimicrobials sold in a country to be used in non-medical purposes and their shares used in agriculture as well as their significance for public healthcare.

In the RF the issue is hardly transparent at the moment although at least two State Strategies stipulate certain plans on how to track antimicrobials used in food production. One of them is the aforementioned federal state information system in veterinary medicine; another is the unified information system for food products tracking which is mentioned in the

Strategy for improving food quality in the RF for the period up to 2030[11]. This will make sources of imported foods more transparent and provide availability of knowledge on antibiotics used to produce them. But the system hasn't been fully developed and implemented yet.

It is also hardly reasonable to rely on a list of standardized antibiotics in food. In the RF they are controlled according to the principles of mandatory priority and voluntary application. It means that mandatory inspections are to be performed regarding residues of antibiotics which are widely used in animal farming (predominantly 1st–2nd generation preparations); other antibiotics are to be inspected only in case there is an application from a food manufacturer[12]. It is impossible to make any correct estimations of the whole range of preparations used in the country since the application procedure lacks credibility and integrity. Therefore, monitoring over AMU can't be equated with a system for goods conformity assessment. To sum up, we can state that it is advisable to use data from the register of veterinary preparations, results produced by veterinary and sanitary inspections which clarify their residues in food raw materials, monitoring results in other countries and scientific publications, especially those focusing on screening of raw materials using multi-residue detection and heat map creation[10] [17].

Medical significance of antimicrobials is an unconditional criterion which should be used when GLIS objects are selected[3] [20]. The Table provides data taken from the WHO list of critically important antimicrobials which are used in medicine, the 6th revision accomplished in 2018.

All antimicrobials in the List are divided into 3 groups according to their significance: critically important, highly important and important. Many of them or their analogues are used in food-producing animals. This leads to selection and spreading resistance to these antimicrobials in animal bacteria, induction of cross and co-resistance which are then transmitted to people with food[3] [11]. This undermines effective antimicrobial use in medicine which is especially dangerous in case of critically important preparations since they are the only available therapy or highly important drugs which are included into treatment standards for treating zoonoses and suppurative infections in people who are able to induce resistance to their agents in non-clinical conditions thus making these drugs completely non-productive and useless.

To reduce health risks caused by use of critically important and highly important antimicrobials in agriculture, the WHO developed recommendations on optimization and best available practices of using them in food-producing animals. These recommendations are based on evidence statistics and are included into the WHO Guidelines [2]. It is recommended to impose complete limitations on use of medically important antimicrobials in food-producing animals:

– all categories, not to be used to stimulate growth and prevent infections which are not diagnosed clinically;

– critically important, not to be used to control clinically diagnosed infections;

– critically important classified as top priority, not to be used to treat clinically diagnosed infections.

Accordingly, for example if chicken meat turns out to contain residues of fluoroquinolones or *E. coli* which are phenotypically resistant to them or DNA-gyrase genes which code resistance to these medications, it means that producers failed to adhere to recommendations on use of quinolones

[11] Strategiya povysheniya kachestva pishchevoi produktsii v Rossiiskoi Federatsii do 2030 g.: utv. rasporyazheniem Pravitel'stva RF ot 29.06.2016 № 1364-r [The Strategy for improving food quality in the Russian Federation for the period up to 2030: approved by the RF Government Order on June 29, 2016 No. 1364-p]. *KODEKS*. Available at: https://docs.cntd.ru/document/420363999?marker=6540IN (December 01, 2021) (in Russian).

[12] Edinye sanitarno-epidemiologicheskie i gigienicheskie trebovaniya k tovaram, podlezhashchim sanitarno-epidemiologicheskomu nadzoru (kontrolyu): utv. resheniem Komissii Tamozhennogo soyuza ot 28.05.2010 № 299 (v red. ot 08.12.2020) [The unified sanitary-epidemiological and hygienic requirements to goods which are subject to sanitary-epidemiological surveillance (control): approved by the Decision of the Customs Union Commission on May 28, 2010 No. 299 (last edited on December 8, 2020)]. *Rospotrebnadzor*. Available at: https://www.rospotrebnadzor.ru/deyatel-nost/tsouz/doc/?ELEMENT_ID=922 (November 29, 2021) (in Russian).

Table

WHO list of Critically Important Antimicrobials for Human Medicine [20]

Medically Important Antimicrobials		Antimicrobial class	Criterion / Prioritization factor (Yes = ●)				
		CRITICALLY IMPORTANT ANTIMICROBIALS	**C1**	**C2**	**P1**	**P2**	**P3**
	Critically important	***Highest priority***					
		Cephalosporins (3rd, 4th and 5th generation)	●	●	●	●	●
		Glycopeptides	●	●	●	●	●
		Macrolides and ketolides	●	●	●	●	●
		Polymyxins	●	●	●	●	●
		Quinolones	●	●	●	●	●
		High priority					
		Aminoglycosides	●	●		●	●
		Ansamycins	●	●	●	●	
		Carbapenems and other penems	●	●	●	●	
		Glycylcyclines	●	●	●		
		Lipopeptides	●	●	●		
		Monobactams	●	●	●		
		Oxazolidinones	●	●	●		
		Penicillins (antipseudomonal)	●	●		●	
		Penicillins (aminopenicillins)	●	●		●	●
		Penicillins (aminopenicillins with ß-lactamase inhibitors)	●	●		●	●
		Phosphonic acid derivatives	●	●	●	●	
		Drugs used solely to treat tuberculosis / mycobacterial diseases	●	●	●	●	
	Highly important	**HIGHLY IMPORTANT ANTIMICROBIALS**	**C1**	**C2**	**P1**	**P2**	**P3**
		Amphenicols		●			
		Cephalosporins (1st and 2nd generation) and cephamycins		●			
		Lincosamides		●			
		Penicillins (amidinopenicillins)		●			
		Penicillins (anti-staphylococcal)		●			
		Penicillins (narrow spectrum)		●			
		Pseudomonic acids		●		NA	
		Riminofenazines	●				
		Steroid antibacterials		●			
		Streptogramins		●			
		Sulfonamides, dihydrofolate reductase inhibitors and combinations		●			
		Sulfones	●				
		Tetracyclines	●				
	Important	**IMPORTANT ANTIMICROBIALS**	**C1**	**C2**	**P1**	**P2**	**P3**
		Aminocyclitols					
		Cyclic polypeptides					
		Nitrofuran derivatives				NA	
		Nitroimidazoles					
		Pleuromutilins					

C1 – Criterion 1. The antimicrobial class **is the sole, or one of limited available therapies**, to treat serious bacterial infections in people.

C2 – Criterion 2. The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that **may be transmitted to humans from nonhuman sources**, or (2) bacteria that may **acquire resistance genes from nonhuman sources.**

P1 – Prioritization factor 1. Large number of people in the community or in certain high risk populations (e.g. patients with serious infections in health care settings), who are affected by diseases for which **there are very limited antimicrobial choices.**

P2 – Prioritization factor *2*. High frequency of use of the antimicrobial class for any indication in human medicine or in certain high-risk groups (e.g. patients with serious infections in health care settings), since their use may favor selection of resistance.

P3 – Prioritization factor 3. The antimicrobial class is used to treat infections in people for which there is already **extensive evidence of transmission of resistant bacteria** (e.g. nontyphoidal *Salmonella spp.* and *Campylobacter spp.*) or resistance genes (high for *E. coli* and *Enterococcus spp.*) **from non-human sources.**

in agriculture thus creating an elevated risk of resistance to them in clinical settings. Therefore, recommendations outlined in these Guidelines should be treated as priority ones in examining all monitoring objects with the focus on products-carriers which are manufactured at relevant stages in food chains (when kettle and poultry are grown for meat, or milk is produced by cows which were treated with antimicrobials etc.).

When assessing risks within monitoring over foodborne antimicrobial resistance, it is also important to determine certain stages in food chains where its transmitters (ARMM, ARMD, or AMU) can occur, spread or be inhibited. The issue is being discussed due to many practical experts trying to confine monitoring solely to food raw materials thus avoiding methodological problems arising when processed foods are controlled including those with mixed compositions even if there are clear recommendations on the necessity to examine them [17].

But international experience shows that control over raw materials allows assessing food contamination with AMRM, AMRD and AMU and managing these risks only when it concerns agricultural producers. It doesn't prevent negative effects produced by these factors during food processing, storage, transportations, sales, imports included, and consumption [21]. Besides, certain technologies applied to process food raw materials (drying, jerking, thickening, or condensation) support AMU residue concentration and do not destroy AMRD. In particular, we were able to detect coliform bacteria resistant to four and eight antimicrobials simultaneously exactly in products ready for consumption (curds and pickle cheese) [9, 10]. Therefore, we can conclude that monitoring over such markers of foodborne antimicrobial resistance as AMRM, AMRD and AMU should cover all food chains up to actual consumption.

Conclusion. Implementation and further development of a system for integrated monitoring and surveillance will result in wider use of their results in assessing actual consumer exposure to such harmful factors as resistant microorganisms and genes, antibiotic residues and risks related to food products being contaminated with them. This can be especially useful for examining antimicrobial resistance, new impacts on food chains, changes in patterns of antibiotic residues in humans and animals, and new testing methodologies.

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