Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

Minutes of the 2nd Stakeholder (SH) Forum

17 September 2019, Istituto Superiore di Sanità, Rome-Italy.

EU-JAMRAI celebrated its 2nd Stakeholder Forum on September 17th, 2019 at the Istituto Superiore di Sanità in Rome. Approximately 120 participants, including key international organizations such as ECDC, EFSA or OECD, representatives from health professionals, patients and industry, health policymakers, Chafea/DG Sante officers, EU-JAMRAI partners and the EU-JAMRAI advisory committee members attended this event.

Marie-Cécile Ploy, EU-JAMRAI coordinator, welcomed and thanked the participants for their involvement and commitment in this fight against AMR and HCAIs. *"The SH is critical for the success of EU-JAMRAI. Your expertise gives an added-value to the JA. We need you to contribute to implementing the EU guidelines to tackle AMR efficiently! We count on you to help us bridge the gap between declaration and action! We need your advices, ideas & recommendations to make this JA a game-changer; we need a behaviour change in both human and animal sectors."*

Charles Price, policy officer on AMR at DG Sante, European Commission, gave the keynote address. He thanked the ISS for hosting this event and the SH for their attendance and commitment. He also thanked the EU-JAMRAI partners and coordinator for the considerable amount of successful work. He highlighted that the JA was studying in detail the barriers and the incentives to turn guidelines into good practices. The ambition of the JA was to sustain the work done in the long-term future. *"The SH has played a key role in bridging the gap between the JA and real action, and that's why we need to support and help them".*

Then, C. Price briefly recalled the history of AMR and the invention of the miraculous drugs. He insisted that for the last 25 years, "*we have been managing diseases without new antibiotics*". We were therefore all concerned, and it was our responsibility to decide what should happen next. There are plans, and some countries made massive progress, but some did not.

He continued stating that ECDC reported in their survey that nearly 100 deaths per day were due to resistant infections in EU-EEA countries. Additionally, the OECD published an economic report with cost-effective solutions showing that full implementation of hand hospital hygiene and AMS could reduce AMR by 16% quickly. C. Price considered that it is a clear message for health systems and he encouraged the EC to do its best to support MSs and SH.

The EC decided to focus on implementation with a 2M€ call to support SH in the implementation of EU guidelines. The European Parliament and the Council also adopted a new EU regulation on veterinary medicinal products on medicated feed. A 30% reduction in antibiotic consumption was observed between 2011 and 2015, but we want to go further, said Charles Price. In June 2019, ministries from all EU MSs adopted the last Council Conclusions on the next steps to make EU the best region for combating AMR.

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In her mission letter, the new Commissioner for Health said: *"I want you to focus on the full implementation of the EU One Health Action Plan against AMR and work with our international partners to advocate for a global agreement on the use of and access to antimicrobials"*. The EU institutions made clear that combating AMR would remain one of the top priority for the coming years. EU countries and SH have also made this a priority. They committed to work together to make the necessary change and achieve this objective.This SH forum is one mechanism through which they can do it.

The SH event was structured in 3 main round tables: (1) Economics models for stimulating innovation and access to antimicrobials, (2) Challenges to antimicrobial stewardship in animal health, and (3) Sustainable integration of the One Health approach in National Action Plans.

FIRST ROUNDTABLE:

The 1st round table was dedicated to **"Economics models for stimulating innovation & access to antimicrobials"** and chaired by **Michele Cecchini from the Organisation for Economic Cooperation and Development (OECD)**. The invited panellists presented their organization and expressed their engagement to support the EU-JAMRAI, which was a complementary action to their missions. The main discussion was:

Mr. Cecchini: Market failure issue is often cited to explain the drying out of the research and development (R&D) pipeline for antibiotics. Is it also the case for diagnostics. In principle, any new effective diagnostic tool making it to the market could be sold without limitations. So, what is missing to create the right conditions for industry to invest in developing new diagnostics to tackle AMR?

Emma Kollatou (MedTech Europe): In general, and from the R&D perspective, there is a lot of innovation in the pipeline in term of diagnostics and medical devices. The aim is to bring more accurate diagnostic tools and to make them available at an earlier stage for the patients. However, there is a lack of recognition concerning the value of our innovation by regulators. Also, the use of diagnostic tools might not be sufficiently incentivized in daily medical practices.

MedTech Europe has been supporting EU level project such as VALUE-Dx or superbug projects, which aim at incentivizing the use of diagnostics for stewardship purpose.

M. Cecchini: Small and Medium Enterprises (SMEs) are the most significant contributors to the AMR R&D pipeline and play a crucial role, particularly in the early phases of the pipeline. Yet, SMEs are among those struggling the most to find capital to invest in promising discoveries. In some cases, even if they are successful, they may end up bankrupt. Can you explain to us the problem? Why are SMEs so vulnerable?

Frederic Peyrane (Beam Alliance): In the AMR field, most SMEs are pre-revenue which means that they have no income. To develop the product, that relies on some public funds and particularly on private investments. To attract private investors, SMEs need to present an attractive exit strategy and demonstrate a return on investment, which is complicated for

antibiotics notably due to low pricing by regulators. A product that regulator does not value will not be worth investing in, despite its efficacy.

M. Cecchini: At the 2016 Davos meeting, more than 100 companies and associations signed the famous "Davos Declaration" which was then followed by a roadmap where companies committed to support open collaboration to work on incentives, pre-competitive collaboration, sustainable clinical trial networks and other interventions that would support R&D. Three years after the release of the roadmap, what are the 'missions accomplished' so far?

Andrea Chiarello (EFPIA): The AMR industry alliance came up with commitments on 4 pillars: Environment, Appropriate Use/Stewardship, Access and R&D. They established concrete ways to track the progress. During the last few years, they have reached interesting milestones and have produced progress reports every two years. Some achievements include:

- a common manufacturing framework for antibiotics which promote responsible manufacturing practices
- the participation of EFPIA in various projects such as PPP, IMI, etc ..
- a call for pull incentives able to delink the revenue from the volume sales. 72% of EFPIA's companies would increase investment on AMR with appropriate pull incentives.

M. Cecchini: The United Kingdom (UK) has launched a trial to test a new payment model for antibiotics. Can you give us more details?

Tracy Parker (Public Health England-PHE):

The UK' trials aims at increasing the revenues from antibiotic sales. 2 news innovative products will be selected and assessed through an improved Health Technology Assessment (HTA) to better value antibiotics. In the end there will be a commercial negotiation of price with annual lump sum based on HTA evaluation and not linked to actual use. The payment will be made whether the drugs are used or not; however there was a nominal price at point of care. The aim was to actively support stewardship and value-based payment.

T. Parker highlighted that doing this project on their own will have no impact on the industry. However, the key goal of the project was to get other countries engaged in supporting and working with the UK.

M. Cecchini: The first primary objective of the Hub was to develop the Dynamic Dashboard. Can you tell us what the Dashboard is and how it was developing? How will the Dashboard help countries supporting the R&D pipeline?

Elmar Nimmesgern (AMR Hub): Dashboard is an IT website to show progress made and to report information on R&D funding and incentives. The target audience was mainly the funders. It was instructive to have a global picture of what was going on in R&D. We want to have a look at institutional funding.

M. Cecchini: How the new Medical Device Regulation (MDR) may influence devices that could be used in the fight against AMR?

E. **Kollatou:** The MDR makes the reprocessing of single-use medical devices more difficult for companies. The current problem is that the MDR has no strict condition for MSs and allows certain hospitals in certain conditions to make use of the reprocess single-use devices. Some specifications are coming in November 2019 to set safety criteria for hospitals.

M. Cecchini: BEAM Alliance has recently released a position paper on supporting financial investments on R&D to de-risk antimicrobial development. Can you tell us your view on the way forward? What can EU countries do to put them in practice?

F. Peyrane: Push funding will not solve the problem. There was a lot of push funding. There is a need to reflect on creating a pull mechanism that creates attractiveness.

The CARB-X model pushes products on the way. So, the solution could be either partnership with CARB-X to have a swift implementation or set up a CARB-X like instrument at the EU level. CARB-X goes until phase 1 but there is a need to support other phases.

M. Cecchini: IFPMA has recently called newly elected EU institutions to work to strengthen the Intellectual Property (IP) framework, as IP rights are one of the fundamental factors to enable further investments on new molecules. What should be the most urgent policy developments to ensure the strengthening of IP rights in Europe? How do you value the set of incentives to support antibiotic R&D currently in place in Europe?

A. Chiarello: The predictability of having IP on invention and innovation is essential. It was time to call on EU institutions to be ambitious on the IP framework for pharmaceuticals. The EC was preparing a report specifically on regulations. The message was to look to all potential ways that we have to incentivize innovation on new antimicrobials, on new vaccines to fight AMR. IP could be part of this solution. There could be some tools based on IP, one in the literature is the Transferable Exclusivity Extensions (TEE) model which could be implemented at EU level. A TEE incentive can be coupled to public health provisions to support access and appropriate use. A central feature of this novel pull incentive is that it does not require upfront or annual government appropriations since the revenue comes from extending current reimbursement of a product to which the TEE is transferred. The ability to sell the exclusivity extension to another company would ensure the incentive is equally applicable to both large pharmaceutical companies with broad portfolios and smaller, more focused biotechnology companies.

There is also an opportunity to couple this new incentive with conditions that make sure that stewardship and appropriate use remain the ultimate objective

M. Cecchini: During the last few months, the Hub has upscaled its activities to collect and harmonize the data to feed the Dashboard. Did you start looking at this evidence? Was there a high-level message or warning signal that can be inferred from what you have found?

E. Nimmesgern: The key message was that investments are made following the One Health approach. One of the concrete examples was JPIAMR that supported around 1900 research projects on animal and environmental health research.

The open discussion was started by **Christine Ardal (EU-JAMRAI WP leader on "Prioritizing and implementing research and innovation for public health needs"),** who visited 10 EU countries to discuss their political willingness and barriers implementing incentives to stimulate R&D. She mentioned that EU countries are thankful to SE and UK for testing the investment models. Pilots are interesting and countries want to see the results and are afraid of examples such as ACHAOGEN, a SME that gathered 450M$ in investment (50% from public funds) and went bankrupt with an innovative antibiotic. What can be done for SMEs to prevent another ACHAOGEN bankruptcy?

F. Peyrane: SMEs have a short timescale. Political decisions have their own timeframe. There is no immediate solution and we are trying to survive; if not we will lose the pipeline.

C. Ardal: There are only 3 large pharma companies that are investing in AMR products. Yet, the drying out of the antibiotic pipeline will influence other products. Without antibiotics, a lot of medical procedures will no longer be considered safe. Why doesn't large pharma companies look at the long-term profitability of antibiotics for oncology?

A. Chiarello: Having solutions to reduce AMR and bring new innovative products to the market doesn't only concern the companies that have anti-infective portfolio, and this was actively discussed with EFPIA. We need more and more companies to care about AMR and to be committed even if they don't have R&D operation' activities in that area of anti-infective or vaccines. EFPIA is exploring novel solutions enabling the value of new and old antimicrobials that should be recognized when it's time for HTA and reimbursement decision.

SECOND ROUNDTABLE:

The 2nd round table was about **"Challenges to antimicrobial stewardship in animal health"** moderated by **Ernesto Liebana from the European Food Safety Authority (EFSA).**

Hein Imberechts (European Joint Programme One Health- EJP One Health) highlighted the importance of having the One Health approach and how it is relevant that EU-JAMRAI is discussing animal health.

He talked about (i) the prevention and metaphylaxis; (ii) the need for Medical doctors to be aware of the vet's problems and the animal's treatment; and (iii) the need to have education programs (for vets and Med students).

There is a lot of discussions to reduce the use of antibiotics (ATB) but there is also a need to take into consideration animal welfare. ATB should be rarely used, but are important to maintain. Thus, the practitioners/vets have to deal with a balance that is not easy to find and challenging when administering treatment. ATB treatment should always follow the correct diagnosis.

FVE mentioned that when the disease spreads rapidly in a flock, it is needed to start treatment before testing.

E. Liebana specified that new EU regulation aimed at stopping preventive use and have clear criteria to be applied when to use metaphylaxis. It is crucial to reduce overall use.

Thierry Chambon (European Veterinary Practitioners Organization – EVPO and Federation of Veterinarians of Europe - FVE) added it was already decided a long time ago to stop preventive use. Metaphylaxis was used only in exceptional cases.

Robert Skov (The International Centre for Antimicrobial Resistance Solutions - ICARS) fully accepts animal welfare, and metaphylaxis to be used when it was needed. The key is ATB management but ATB are too cheap to subsidise good management. Also, many vets have a part of the salaries in selling ATB. In Denmark, there was a market-driven initiative on producing pigs without ATB. They succeed and, in those farms, 80% of pigs were produced without ATB. It is a marginal production marketed "Grown without ATB" and sold at a higher price.

Rens Van Dobbenburgh (FVE and European Platform for the Responsible Using of Medicines in Animals - EPRUMA) added that all meat in EU is ATB free because animals are killed in a specific way, with delay for marketing after treatment.

H. Imberechts added that the use of ATB cannot be radiated entirely, and should be reduced and used correctly. Practitioners need good guidelines and/or incentives to use less ATB.

T. Chambon commented on the legislative measures that can help to fight against AMR, but vets did not wait for any improvement in the legislation. Voluntary actions enabled a large reduction of ATB consumption in all the EU member states. Now EU legislation was published in 2019 just harmonising practices at the EU level. In addition, recommendations are the starting points in improving legislation. FVE was working at the global level and represent associations from more than 40 countries. Very useful guidelines were developed within FVE to be implemented at the local level.

Rodolphe Mader (Anses, France) indicated that countries that separated selling from prescription did not always have best results in reducing prescription. In France, it was managed to reduce ATB use.

He added that the impact of ATB free animals or meat is good but the consumer misleads on “ATB free” as they think that other meat is “ATB full”. There is a need to communicate more and foster this animal production but we need to accompany communication to avoid that ATB free meals become a business.

Charles Price (DG Sante) said that there is a 3 times difference in human use across EU, but 100 times differences between countries with lowest sales of ATB per population unit and countries with highest sales (source EMA). In animal health, the legislation is unified at EU level.

R. Van Dobbenburgh underlined the high responsibility for the vet profession of being seller and prescriber.

Maria Jaureguizar (The Vet+i Foundation, Spanish Technology Platform for Animal Health - Vet+i) specified that it was mandatory for vet to notify the prescription of ATB in Spanish farms.

R. Skov gave the view on the use of critical antibiotics (CA) in the treatment of animals. There are two sets of lists in human and vet use that are produced differently. The CA are mostly referred in the WHO list. He underlined the importance of prudent use of ATB. Data are lacking on what is more damaging or less damaging. There is a need for both the existing global list and another one taking the local situation into account; thus the new EMA categorization was different from the global list.

R. Van Dobbenburgh talked about the actions that veterinary profession already takes to tackle AMR. They always support projects to understand the mechanism behind AMR, and promote the implementation of best practices, nutrition, vaccination, etc.. They care for solutions for animals: they collaborate with CPME, CED, PGEU and communicate with SH like the EU-JAMRAI event and EU institutions to teach them about AMR in animals and how to fight.

As the outcome of these actions, R. Van Dobbenburgh reported that there was a decrease in ATB use in some countries as Germany, Belgium and Netherlands.

R. Van Dobbenburgh highlighted the need for a good implementation of EU legislation and balanced approach Human/vet as actions for the future.

M. Jaureguizar presented the Vet+i's goal on the issue of the responsible use of medicines, including ATBs in Spain and its achievements. They are acting as a bridge between all stakeholders in Spain from public and private sides, and work together since 2008 to move forward. In 2013, they developed an initiative on a responsible use of vet medicines following a holistic approach. They explain responsible use to vets through training, communication of guidelines and social media.

EJP highlighted the need for the One Health approach. In different Members States, intersectoral committees should know each other and act together to be strong together.

Only EU initiatives exist that help to align approaches, to share databases, to discuss together on scientific projects on new resistances, emerging germs, diagnostic tests, etc.. There is a need for these EU approaches not only for science, to be aware of what is happening timely, but also to come up with solutions on how should this data will be integrated. There are already some initiatives in different countries, but they should be reinforced. Thus, the Joint programme EJP One Health that strengthens collaboration between institutes by enhancing transdisciplinary cooperation and integration of activities using dedicated Joint Research Projects, Joint Integrative Project and through education and training.

THIRD ROUNTABLE:

The final session was focused on **"Sustainable integration of the One Health approach in National Action Plans (NAP)"** moderated by **Charles Price (AMR policy officer. DG SANTE)**.

Celine Pulcini (EU-JAMRAI WP leader on sustainability and coordinator of the French NAP on AMR in the French Ministry of Solidarity and Health) presented the sustainability plan of the EU-JAMRAI that will be developed based on two major actions:

- Integration: uptake of the EU-JAMRAI outputs at MS' level (national, local, regional) into, for example, national policies, national actions/programmes, by different actors (government, professionals…)

- Sustainability: strategy defining which EU-JAMRAI elements/deliverables/results will be further developed, consolidated or run and by which organisation this will/should be done.

She detailed the priority goals and EU-JAMRAI key actions.

Dominique Monnet (ECDC) said that ECDC is seen as a stakeholder to take on board all outputs. ECDC was willing to host links on ECDC website and happy to advertise documents produced.

He underlined that ECDC has a (i) mandate for Human health so they cannot advertise for animal health and (ii) mandate for risk assessment and risk communication but not risk management.

Besides, he reflected that there are many networks (One Health Network (OHN), Health Security Committee (HSC), ECDC surveillance networks). However, EU-JAMRAI is somewhere in between, which means that EU-JAMRAI could discuss policies, intervention, and implementation as a more technical level than the OHN. Another element of the sustainability of EU-JAMRAI could be to create a network that is linked and worked with other networks.

Ann Marie Borg, European Public Health Alliance (EPHA): AMR stakeholder network already exists under EPHA's aegis within EC health policy platform. There are a lot of discussions but hard to move forward and they want to know how to use the outputs and have better use of this network.

For the mapping of NAP and strategies on AMR, EPHA realised that there is a fragmentation of information on different websites. However, there is a need to have one AMR portal, including the contact details of AMR representatives. Some missing information is required to knwo how to support the implementation of NAP and the funding opportunities.

C. Price commented on the importance of being in touch with the national focal points to have all the needed information.

Jan de Belie (PGEU) mentioned that he is eager to ensure that outputs transferred to national membership of EU associations.

D. Monnet is aware that professional associations have a problem to liaise with national representatives, but ECDC cannot put the name of National AMR coordinator for RGDP reasons for the moment.

Enrique Castro-Sanchez (European Specialist Nurse Organisation - ESNO) collaborates on defining the core competencies on antimicrobial stewardship and on Infection and Prevention Control. ESNO is engaged in supporting the sustainability of the EU-JAMRAI and mobilising the political players as 2020 is the year of the nurses.

Mary McCarthy (European Union of General Practitioners - UEMO) reminded that sustainability is a team effort that involves all members of healthcare professions, including general practitioners who prescribe the drugs and nurses who explain to patients how to get them. She talked about some elements to be considered in the sustainability plan: (i) the need to recognise the workforce pressure; (ii) the lack of consultation time to explain to patients why they don't need antibiotics and the need to protect legally if no prescription; (iii) the necessity of adequate guidelines in case of adverse events; and (iv) the multi pathology of the population thus the lack of time for doctors to manage these complex cases.

Ernesto Liebana (European Food Safety Authority - EFSA) underlined the need of integration that it is EFSA's DNA. The risk assessment and surveillance are conducted with ECDC.

He joined D. Monnet and underlined the need to invest in the OHN to expand its actions.

EFSA is committed to increasing the flow of information between the stakeholder forum. He highlighted that relevant stakeholders and key players in food safety and animal sector from EC are missing in the EU-JAMRAI. EFSA promises that JAMRAI work will not be lost.

He added that evidence to support policy is an old debate. After years of doing quantitative modeling, it seems impossible not to act. We have some evidence and cannot wait to have a full scope of evidence to do something.

Laura Marin (JPIAMR) followed the discussion by adding that JPIAMR finances and supports research on the AMR field. Within EU-JAMRAI, they proposed a dialogue between all actors.

Jean-Baptiste Rouffet launched a challenge encouraging the stakeholders to take one or two actions:

- C. Price started this challenge and said that the network of supervisory bodies is a great idea and he committed to talking at the EC about it.

- EPHA committed to disseminate the EU-JAMRAI work and documents on EPHA's website, to help setting an EU network. Regarding the surveillance, they would act as an advocacy role for EU-wide targets.
- UEMO committed to keeping the essence of cooperation.

Jérôme Weinbach (The French Ministry of Solidarity and Health) wrapped-up the SH forum.

He underlined that there are still barriers due to corporate positions. The EU-JAMRAI brings solutions on how to work together in a One Health approach, and has already concrete deliverables to bring to the community. Thus, we have to overcome these barriers if we want to work together in this global approach. It is not always a question of money, but about collective responsibilities, we commit for the future generation. For instance, it is better to invest in public-private partnership and there is a need to build capacities with industry.

The timeframe is different from SMEs. There are some tools offered by the governments and the EC. Concerning the agencies, he highlighted the importance of cooperating in a transectorial approach.

He remembered the role of the SH forum regarding the EU-JAMRAI sustainability to pass the good message serving the One Health approach, and ask their relative governments to support the continuation of the EU-JAMRAI handover and commitment, and to secure for a good and sustainable network. All of us need to continue this work together and to take action!