Call for a Sound Management of Pharmaceutical Waste and Wastewater to Curb Antimicrobial Resistance

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Abbreviations and acronyms

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
API	Active pharmaceutical ingredient
BAT	Best Available Techniques
EPP	Environmentally preferable purchasing
EPR	Extended Producer Responsibility
FAO	Food and Agriculture Organization
GAP	Global Action Plan
GLASS	Global Antimicrobial Resistance Surveillance System
GMP	Good Manufacturing Practices
HCWM	Health-care waste management
HAI	health-care-associated infection
HIV	human immunodeficiency virus
IPC	Infection Prevention and Control
MBR	Membrane Biological Reactors (MBR)
MBBR	Moving Bed Bio Reactor
MDR	Multidrug-resistant
MoH	Ministry of Health
NAP	National Action Plan
OIE	World Organization for Animal Health
SEA	South-East Asia
SDGs	Sustainable Development Goals

UN	United Nations
UNEP	United Nations Environment Programme
UNGA	UN General Assembly
UNICEF	United Nations Children's Fund
WASH	Water, Sanitation and Hygiene
WHA	World Health Assembly
WHO	World Health Organization

1 GLOBAL AND REGIONAL CONTEXT

A 2012 report of the World Health Organization (WHO) stressed the importance of prioritizing the emerging issue of pharmaceuticals in drinking water in the overall context of water safety management, including microbial and other chemical risks that may threaten the safety of drinking water (WHO 2012). In 2015, in recognition of the growing problem posed by the unwanted presence of pharmaceuticals in the environment, the UN Strategic Approach to International Chemicals Management (SAICM) identified the role and responsibilities of the health sector in reaching the SAICM 2020 goal for sound chemicals management[4].

Antimicrobial resistance (AMR) is one of the most complex public health threats the world has faced. In 2015, the World Health Assembly (WHA) endorsed a global action plan (GAP) to tackle antimicrobial resistance, including antibiotic resistance. One objective of the AMR GAP is to improve infection prevention and control (IPC) by ensuring the provision of safe and sustained water, sanitation, and hygiene services (WASH), including the sound management of healthcare waste (WHO 2015; WHO 2016). These efforts are in line with the targets of the UN Sustainable Development Goals (SDGs), particularly of SDG 3 on health, SDG 6 on safely managed water and sanitation and SDG 12 on sustainable consumption and production.

In 2016, a high-level meeting on AMR was convened during the UN General Assembly (UNGA) at which global leaders committed to address the challenge via the "One Health"

[4] "Strategic Approach to International Chemicals Management: implementation and priorities in the health sector", http://www.euro.who.int/__data/assets/pdf_file/0015/303036/SAICM-meeting-report-en.pdf

approach. Indeed, no single government department or independent organization can tackle it alone. Containing and controlling AMR demands coordinated action across diverse sectors and disciplines, with a broad range of stakeholders. They also called for action, and outlined initiatives carried out nationally to address AMR. (WHO, 2018).

The pharmaceutical industry committed to establishing the "AMR Industry Alliance", which includes biotechnology, diagnostics, generics and research-based pharmaceutical companies and associations, to drive and measure the life sciences' industry progress to curb antimicrobial resistance.[5] The Alliance signed the Industry Declaration on AMR at the World Economic Forum in 2016, followed by the adoption of a Roadmap.

Since 2010, the WHO Regional Office for South-East Asia (SEARO) has recognized AMR as a serious threat to public health. Regional Committee sessions and other high-level forums have adopted and issued several resolutions and declarations on its prevention and containment. Of note is resolution SEA/RC/63/R4 adopted at the Sixty-third session of the Regional Committee in Bangkok, Thailand, in 2010, and the Jaipur Declaration on Antimicrobial Resistance by the Health Ministers of the Region issued in 2011 (WHO SEA, 2016). In 2014, AMR was included as a "Regional Flagship Priority" by the SEARO Regional Director. The Regional Director called for building national capacity to combat AMR, with a focus on achieving clear deliverables at both the regional and country levels. In 2016 the Asia Pacific "One Health Initiative on AMR" reaffirmed its commitment to end

[5] AMR Industry Alliance: https://www.ifpma.org/partners-2/declaration-by-the-pharmaceutical-biotechnology-and-diagnostics-industries-on-combating-antimicrobial-resistance-amr/

AMR and emphasized the need for a coordinated, multisectoral One Health approach. In line with WHA GAP, SEARO developed a regional roadmap to guide Member States in developing national AMR prevention and containment via National Action Plans (NAP), which all 11 WHO SEA Member States[6] have developed.[7]

Aim of this policy brief: The policy brief is intended as a tool to guide establishing regulatory frameworks to ensure the sound management of pharmaceutical solid and liquid waste. The guidance document is to be used by WHO staff, policy makers and inspectors in Ministry of Health (MoH) and Ministry of Environment, pharmaceutical manufacturers and their associations, local municipalities and consumer organizations.

2 DEFINITION AND GENERATORS

Pharmaceuticals are indispensable for human and animal health as these are used to diagnose, cure, treat, and to prevent disease. Pharmaceuticals can end up in the environment when released from manufacturing sites, health care facilities, and individual households and from animal industry. Indeed, in many countries of the SEA Region, pharmaceuticals are misused to promote animal growth by feeding antibiotics to prevent diseases and ensure animal growth..

WHO defines pharmaceutical waste as follows: “Pharmaceuticals that are expired or no longer needed; items contaminated by or containing pharmaceuticals and cytotoxic waste

[6] Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste

[7] Library of national action plans: http://www.searo.who.int/entity/antimicrobial_resistance/national-action-plans/en/

containing substances with genotoxic properties, e.g. waste containing cytostatic drugs (often used in cancer therapy); genotoxic chemicals" (WHO 2014a). Under the Basel Convention "waste pharmaceuticals, drugs and medicines" are classified as Y3 waste (UNEP 1989). Such waste includes: analgesics / pain killer, vaccines and sera, antimalaria drugs, controlled substances (i.e. narcotics, psychotropic substances), endocrine-disrupting pharmaceuticals (hormones) and antimicrobial agents including antibiotics.

Specific pharmaceutical substances are not metabolized and remain active in the environment after disposal. Waste of antimicrobial pharmaceuticals can lead to Antimicrobial Resistance (AMR) via genetically transmitted antibiotic resistance. AMR has become a worldwide risk for humans and animals as it threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. As a result, standard antimicrobial treatments – including antibiotics – become ineffective, infections persist and may spread to others (WHO 2016a). Waste containing endocrine disrupting pharmaceuticals can adversely influence the hormone system of humans and animals. Cytotoxic drugs and genotoxic chemicals are antineoplastic drugs. The waste is toxic to living cells by design and toxic in low concentrations.

There are 3 groups of pharmaceuticals that are particularly active in low concentrations and therefore need special attention of researchers and policy-makers:

i) antimicrobial pharmaceuticals

ii) endocrine-disrupting pharmaceuticals and

iii) cytotoxic drugs / genotoxic chemicals (antineoplastic drugs).

(Source: Kümmerer 2010)

Pharmaceutical waste is generated by pharmaceutical manufacturing, the animal industry, research institutes and from use in humans. During emergencies major quantities of pharmaceutical waste can be generated by donations that are already expired before or become expired after they reach the emergency area (WHO 1999).

Sector	Settings
Pharmaceutical manufacturers & research institutes	Human medicine, veterinary medicine
Human health	Health facilities, medical practice, nursing homes, pharmacies, households
Animal health and growth promotion	Animal farms (agriculture and aquaculture), veterinaries, pharmacies, pet holder

Table 1 Pharmaceutical waste generators

3 ENVIRONMENTAL AND HEALTH IMPACTS

Properly managed pharmaceutical waste does not represent a threat to public health or the environment. It becomes a threat when it contaminates the environment or when obsolete drugs find their way back to the informal pharmaceutical market. In South Asia, reusing syringes and needles is still a frequent practice and is a public concern (Uddin et al, 2017). Pharmaceutical substances can enter the environment via different pathways:

- Release of solid and liquid pharmaceutical effluent waste from manufacturing facilities and research institutes. Accidental spills during manufacturing or distribution are another source of water contamination.

Example India: India is a major producer of generic medications and active pharmaceutical ingredients. Of 34 pharmaceutical manufacturing sites tested, 16 were found to be harbouring bacteria resistant to antibiotics. At four of these sites, resistance to three major classes of antibiotics was detected, including carbapenems*. The pharmaceutical companies involved export antibiotics to several countries including high income nations such as the UK, USA, and France (Changing Markets 2016).

*Carbapenems are a class of highly effective antibiotic agents commonly used for the treatment of severe or high-risk bacterial infections. This class of antibiotics is usually reserved for known or suspected MDR bacterial infections.

- Excreted pharmaceuticals resulting from human/animal health treatment and growth production can enter the wastewater or surface water system.
- Veterinary pharmaceuticals that are directly discharged in waterbodies as when applied in aquaculture.
- Disposal of leftover medicines in toilets from households entering the waste water system or surface water.
- Untreated or poorly treated wastewater may contain concentration of active pharmaceutical substances and resistant bacteria, which will enter the water system.
- Sludge from wastewater treatment contaminates soil mainly by manure spreading in the fields and then by run-off and leaching, surface and ground water.
- Improper disposal on unsecured landfills or dumpsites may contribute to ground water contamination by leaching.
- Finally, contaminated surface and ground water may reach drinking water treatment plants. Some active pharmaceuticals can thus reach tap water or the food chain and return back to humans, animals and pharmaceutical production (orange arrows in the figure below).

The figure summarises how various often-interlinked factors contribute to contamination of the environment, with the transfer of pharmaceutical residues and antibiotic resistance bacteria and genes back to the human and animal health system.

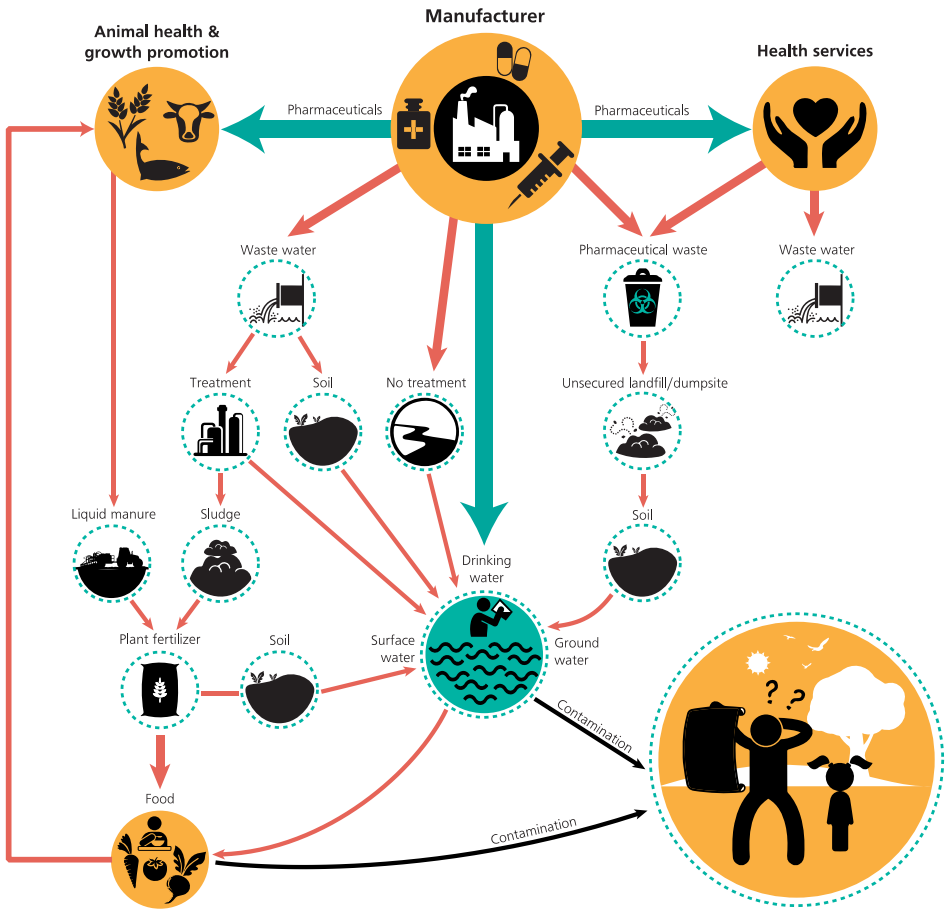

Figure 2: Key risks and key pathways of environmental routes potentially boosting AMR.

Notes:

1. The Manufacturer, Humans and Animals are generating solid and liquid waste – in the figure these are in one box as these are all the generators. The arrows are coming arising from the complete group as well as the orange arrows are going back to the complete group of generators.

2. Manufacturers may be the main producer in some regions of SEA - in others it is very likely that the main producers are from human excretions. However as long no mapping and assessment has been conducted this is an open area. “The consumption phase is the biggest contributor to the emissions of medicinal products into the environment, notably through excretions and incorrect disposal of unused medicines through sinks and toilets. Between 30 and 90% of the orally administered dose is generally excreted as active substance in the urine of animals and humans”.

https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf

Once pharmaceutical substances enter the environment and contaminate ground and surface water it may reach drinking water sources. These substances may be taken up by aquatic animals like fish, accumulating through the food chain to end up as food. Since the mid-1980s scientists have increasingly reported about traces of pharmaceuticals in the environment. Endocrine disrupting substances drew special attention in the 1990s but were also referred to as a main issue recently in the 2019 European Union Strategic Approach to Pharmaceuticals in the Environment[8]. At the time, public debate also focused on the environmental impact of residues of contraceptive hormones on the environment. The awareness about pollution of the environment by antimicrobics in general, and of aquatic ecosystems, along with the presence of antibiotic resistant bacteria and resistance genes in aquatic ecosystems, is increasing globally. Antibiotics are one of the most common medicines in hospitals and the community. The potential presence of active antibiotics in drinking water sources is of concern due to the

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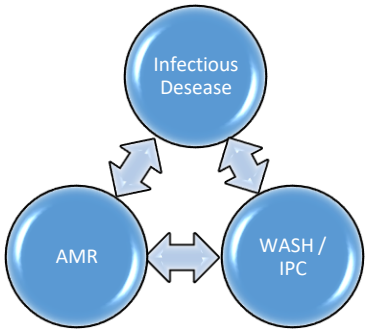
http://ec.europa.eu/environment/water/waterdangersub/pdf/strategic_approach_pharmaceuticals_env.PDF

unknown health effects of chronic low-level exposure to antibiotics over a lifetime. As bacteria replicate quickly, the resistant bacteria that enter water bodies through wastewater replicate their resistance genes as they continue to divide. In addition, bacteria carrying resistance genes have the ability to spread those genes to other species via horizontal gene transfer. Therefore, even if the specific antibiotic is no longer introduced into the environment, antibiotic-resistance genes will persist through the bacteria that have since replicated without continuous exposure (Martinez & Olivares 2012).

The more antimicrobial drugs are produced and misused the more resistant microorganisms (bacteria, fungi, virus, protozoa) will arise. Many of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug-resistant (MDR) forms subsequent to antibiotic use. AMR microorganisms can be passed between humans and animals but also via other pathways in the environment. Complex interactions amongst environmental- and health-related factors contribute to the spread of antimicrobial resistance. Careless Water, Sanitation and Hygiene (WASH) practices, including poor waste management and lack of compliance with Infection Prevention Control (IPC) standards measures, have contributed to the propagation and spread of resistant strains. This will result in an increasing number of resistant infectious diseases that can no longer be treated by conventional antimicrobial drugs.



If this trend continues, it is estimated that by 2050, 10 million lives a year and a cumulative US$ 100 trillion of economic output are at risk due to the rise in drug-resistant infections (WB 2017; O'Neill 2016).

4 ADAPTING TO CLIMATE CHANGE

The increasing global ambient temperatures that are driving climate change affect the hydrological cycle and adversely impact health. This is because temperature and precipitation influence many communicable and noncommunicable diseases that are related to the quality and quantity of water. Diseases affected by climate change via water include food-, water- and vector-borne diseases, and the health consequences of undernutrition if crops fail due to droughts (WHO 2017). Countries in the WHO SEA Region are particularly vulnerable to the changing climate (Bowen, Kristie 2017).

> The Fifth Assessment Report of the Intergovernmental Panel on Climate Change notes that it is very likely that the mean annual temperature increased over the past century over most of Asia. For most of Southeast Asia, annual temperatures over the past 100 years increased by approximately 0,6 °C per decade. The projected temperature for Asia in the middle and at the end of the century depends on the pathway for emission of greenhouse gases, with an upper estimate of more than 6 °C. It can be predicted that heavy precipitation events are increasing, and light rainfalls are decreasing. In south Asia, seasonal mean rainfall has declined, with more frequent deficit monsoons. Precipitation extremes related to the monsoon are projected to increase in south and south-east Asia, with precipitation likely to become more extreme near the centres of tropical cyclones making landfall (Hijoka et al 2014).

Climate change-related extreme weather events can be harmful for the existing water distribution and waste management infrastructure due to flooding or damaging of landfills and wastewater plants/pits. Increased temperature will have a direct impact on the reaction rate of biological wastewater treatment processes which can become less effective or simply disabled.

Adaptation and mitigation are needed. This includes:

- Reducing both greenhouse gas emissions and power consumption.
- Practicing sustainable procurement and waste reduction.
- Developing climate resilient water, wastewater and waste safety plans.

- Establishing of “greener” (like rain gardens or reed beds that treat wastewater) and adapted “grey” human-engineered infrastructure.
- Planning of new landfills and wastewater plants at higher elevations.

5 MANAGEMENT OF PHARMACEUTICAL WASTE

5.1 Managing supply chains to minimize pharmaceutical waste

To assess the significance and act upon the environmental and health dimensions and impact of liquid and solid waste, the generation sources and waste volume need to be mapped at the national level. The used pharmaceuticals should be earmarked based on their toxicity of the active ingrediency, the risk for the environment and health as well as the ease of degradability as solid waste and as waste in water. Based on the results, “hot spots” can be identified, at which immediate measures would need to be taken based on an action plan for the sound management of pharmaceutical waste. One source is the “Antimicrobial Resistance Benchmark 2018” report, which provides an analysis of pharma company action against AMR, covering antimicrobial R&D, responsible manufacturing and appropriate access and stewardship (Access to Medicine Foundation 2018). A key supporting tool is the WHO Global Antimicrobial Resistance Surveillance System (GLASS), which provides a standardized approach for the collection, analysis and sharing of data related to antimicrobial resistance at a global level to inform and drive decision-making at local, national and regional levels (WHO 2015b).

The best strategy to reduce pharmaceutical waste is avoidance by reducing unnecessary procurement, dispensing, overuse, misuse and supply of medicines. Good Manufacturing Practices (GMP) by manufacturers should include environmental aspects of appropriate pharmaceutical waste disposal. GMP should guide on how to treat pharmaceutical effluents before they are discharged as wastewater to minimise the release of antimicrobials to the

environment. Public awareness is a key component to reduce the misuse of pharmaceuticals. By implementing safe IPC and effective WASH interventions, including proper waste management practices, infectious diseases can be reduced and therefore the application of pharmaceuticals – especially antimicrobials – and the generation of waste thereof, can be decreased.

Pharmaceutical waste can be minimized using efficient inventory controls or a "just-in-time" inventory strategy; by purchasing drugs at the dosages routinely administered; by always monitoring expiration dates to reduce the risk of stockpiling obsolete pharmaceuticals (First In, First out FIFO principle); by replacing pre-packaged unit dose liquids with patient-specific oral doses; and other good management practices (WHO 2014).

Sustainable or environmentally preferred purchasing (EPP) refers to the purchase of the least damaging products and services, in terms of environmental impact. The implementation of EPP and joint and standardised procurement leads to lowering the environmental and social impact of procurement. The joint UN Procurement project is an example of procurers working with supply companies to shift towards procuring more sustainable products.[9]

If feasible, pharmaceuticals within their expiry date and considered useful should be separated out and immediately used by the institution or reallocated according to the needs and instructions of the health authorities. An interactive list can be prepared giving details of the items available, quantities and expiry dates and circulated to others who can use the materials.

The pharmaceutical industry's accountability for the impact of their products should not end at the point of sale. The Extended Producer Responsibility (EPR) concept aims to promote the

[9] United Nations Informal Interagency Task Team on Sustainable Procurement in the Health Sector (SPHS): https://savinglivesustainably.org/

integration of environmental costs associated with goods throughout their life cycles into the market price of the products (OECD 2001). It is important to tackle the serious impacts of pharmaceutical pollution on the environment, and to include key measures to address these in the strategic approach on Pharmaceuticals In the Environment (PiE) (EC 2017, EC 2018). PiE was first introduced in Sweden in the 90's and was then inserted in several strategic documents and guidance's of UN organizations, including WHO. Pharmaceuticals should be kept in their original packaging to aid identification and prevent reaction between incompatible components (WHO 2014). Manufacturers should contribute to finance collection/take-back schemes. Such schemes should be harmonised and expanded across the Region to prevent unused pharmaceuticals from reaching the environment. For unwanted, unrequested donations, especially those that arrive past or unreasonably near their expiry date the possibility to return them to the donor for disposal should become obligatory (WHO 1999). PiE could be adapted to be implemented to the pharmaceutical sector in SEAR.

Once pharmaceutical waste is generated it needs to be safely managed and in an environmentally friendly way. In the South East Asia Region it is essential that countries develop comprehensive health care waste management strategies and improve and maintain sufficient capacity to appropriately destroy and prevent contamination of the environment by pharmaceutical and especially antimicrobial waste.

5.2 Sound solid pharmaceutical waste management

The objective of sorting is to separate the pharmaceuticals into separate categories for which different treatment/disposal methods are required. The segregation should be made into those that can be safely used and returned to the pharmaceutical supply system and those that require disposal by different methods. For example, controlled drugs (e.g. narcotics), antineoplastic

drugs and antibiotics all require special methods of treatment and disposal (WHO 2014a). Pharmaceutical waste with non-hazardous characteristics like vitamins, amino salts, salt solutions etc. can be disposed as general household waste, but it must be ensured that the waste cannot be claimed by the informal sector and sold without professional supervision. Liquid chemical wastes should never be mixed or disposed of down the drain but should always be stored in strong leak-proof containers. Packaging material such as waste paper/card boxes and wooden items such as pallets, can be recycled, or treated/disposed of as general household waste.

Hazardous pharmaceutical waste should be treated via Best Available Technics (BAT) like modern high temperature incinerators with flue gas treatment (UNEP 1989, UNEP 2012). Expired or unused vaccines can also be treated via alternative non-combustion technology such as autoclaving. Trained specialists only should conduct chemical decomposition. In low-resource settings, encapsulation is an option, but should be followed by an improvement strategy.

Pharmaceutical waste can be disposed in a secured landfill or first immobilised by encapsulation or inertization and then landfilled. A well-engineered landfill is designed to minimize contamination of soil, surface water and groundwater; limit atmospheric releases and odours; block access to waste by pests and vectors; and prevent contact with the public (WHO 2014). Controlled substances (e.g. narcotics and psychotropics) require tight security and control. In some countries, scavenging of material from landfills is a frequent problem, and, disposed drugs may be recovered and sold by the scavengers. Measures are therefore necessary to prevent diversion during sorting, and pilfering of drugs from landfills. Expired pharmaceuticals in health facilities or in warehouses pose the risk of being repackaged and re-entered illegally into supply chains. Well-controlled disposal procedures for expired antimicrobials are essential. Immobilization is the best method of preventing pilfering from an unsecured store or landfill. If,

as a last resort, pharmaceuticals must be discarded direct to an unsecured landfill or dumpsite then they must be covered immediately with a large quantity of municipal waste (WHO 1999).

5.3 WASTEWATER MANAGEMENT

Liquid pharmaceutical waste in wastewater may evolve into a serious problem and must be carefully observed and where possible diminished. This includes reducing the presence of antibiotics and pharmaceutical residues in wastewater to an absolute minimum (WHO 2014b). Antibiotics and their metabolites are disposed by the manufacturers or excreted with urine and faeces and end up in the waste water stream. Hospital waste waters are a source of bacteria with acquired resistance against antibiotics with a level of at least a factor of 2 to 10 times higher than in domestic waste water. There is increasing evidence that waste water treatment plants are hotspots that sustain and further promote the propagation and selection of antimicrobial-resistant bacteria and AMR genes within their systems as well as function as major point sources that release them into the environment, where they disperse (WHO 2014c; WHO 2012). The situation is worse in SEA countries as over 80% of the waste water is not treated at all and contaminates ground water, surface waters, soil, and even crops (WEPA 2012). Concentration limits of antimicrobials and endocrine disrupting compounds in drinking and waste water need to be established and compliance enforced by the relevant authorities through regular monitoring. Central and decentralised wastewater treatment technologies need to be improved at manufacturing sites and at hospitals. Cytotoxic waste and genotoxic drugs (antineoplastic pharmaceuticals) should not enter the waste water system as they may damage aquatic life or contaminate drinking water – this need to be incinerated by state-of-the-art high temperature equipment. Technologies that remove or destroy pharmaceutical contaminants in waste water should be further developed and emission limits continuously lowered. Various studies have evaluated the effectiveness of wastewater treatment on the removal of antibiotic-resistant

bacteria and resistance determinants (Fletcher 2015, Rizzo at al 2013). There is evidence that the efficiency of removal is dependent on antibiotics' physicochemical properties and the operating conditions of the treatment process (Rizzo at al 2013). Currently different advanced treatment technologies like Membrane Biological Reactors (MBR), Moving Bed Bio Reactor (MBBR), UV radiation and chlorination are examined. Further research is needed (Fletcher 2015; AUH 2018).

6 KEY RECOMMENDATIONS

1. Mapping and surveillance of the potential environmental risks of all pharmaceuticals in the SEA region. This should include surveillance of antimicrobial resistance and monitoring of the prevalence of, and trends in, resistance in bacteria from humans, animals, food and the environment.

2. Develop comprehensive national legislative framework and financed implementation in all WHO SEA countries including waste and water safety plans with accountability and civil society engagement to reduce the impact of pharmaceuticals on the environment.

3. Enhance Good Manufacturing Practices by including environmental criteria, developing guidance for waste solid and liquid waste management and include compliance as a condition for licensing of pharmaceutical manufacturers and distributors.

4. Enhance the sustainable procurement, supply chain and inventory management pharmaceuticals, including green procurement to reduce pharmaceutical waste and switch to pharmaceuticals with a lower environmental impact.

5. Introduce Extended Producer Responsibility: make the pharmaceutical industry accountable for pharmaceutical waste throughout the life cycle.

6. Foster innovation and research & development for new approaches and tools to reduce and improve pharmaceutical waste and improve wastewater management in low-resource settings from all sources (health care, manufacturing, agricultural waste).

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