

Removal of antibiotics and pharmaceutical residues in water urgent

| WHITEPAPER

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Dutch Consortium Antibiotics and
Pharmaceutical Residues from Water





Summary

According to the WHO, antimicrobial resistance (AMR) is one of the greatest threats to health and food safety. It is increasingly evident that antibiotics, resistant micro-organisms, and their resistance genes are spreading invisibly through water. It is important that we tackle AMR effectively in water too.

Antibiotics and other medicines will continue to play a key role in our everyday lives, therefore the demand for technologies to reduce AMR in water will increase on a global scale. **By investing in sustainable innovative technological solutions for AMR now, we can avoid paying the costs of the damage that AMR and other drug residues will cause to our society.**

Besides, it is important to focus on responsible antibiotics prescription, especially in countries where prescribing behavior is excessive. With this approach we can reduce antibiotic and medicine residues in surface water. However, the largest part of the residues of medicines in wastewater comes from 'regular' households. Calculations by the Dutch National Institute for Health and the Environment (RIVM) show for instance that every year in the Netherlands at least 190,000 kg of medicine residues from urine and faecal matter end up in surface water and groundwater. These residues pose a risk to drinking water. Some of these residues, such as hormones, various painkillers, some anti-epileptic drugs and psychopharmaceuticals have a disruptive influence on the plants and animals living in the water.

In addition, a significant proportion of antibiotics in water come from hospitals. **Because in hospital wastewater the concentrations are relatively high, removal of these antibiotic and medicine residues 'at the source' is most effective.** Then we can prevent further resistance formation, spread of resistance genes and ecological damage. In hospitals, many so-called 'last resort' antibiotics are frequently used. These are of vital importance for the recovery of patients with multi-resistant infections. By also removing these antibiotics at the source, we prevent bacteria from becoming resistant to 'last resort' antibiotics as well.

Through better cooperation between the pharmaceutical sector, health care and the water sector, it will be possible to significantly reduce the existing antibiotic and medicine residues in wastewater and surface water. In the Netherlands, the government adopted the 'Chain Approach Medicine Residues from Water' policy. The chain approach has recently been nominated by the 'World Future Council' for the Future Policy Award 2021. **The "Dutch Consortium on Antibiotics and Pharmaceutical Residues from Water" consisting of a 'coalition of doing' acts in accordance with this chain approach and specifically focuses on the removal of antibiotic residues from water.** Together with other chain partners, this Consortium aims to deploy and, where necessary, develop the most sustainable and effective solutions.

Problem description

Antimicrobial resistance

The COVID-19 virus shows that a single micro-organism can disrupt society and damage economies worldwide.

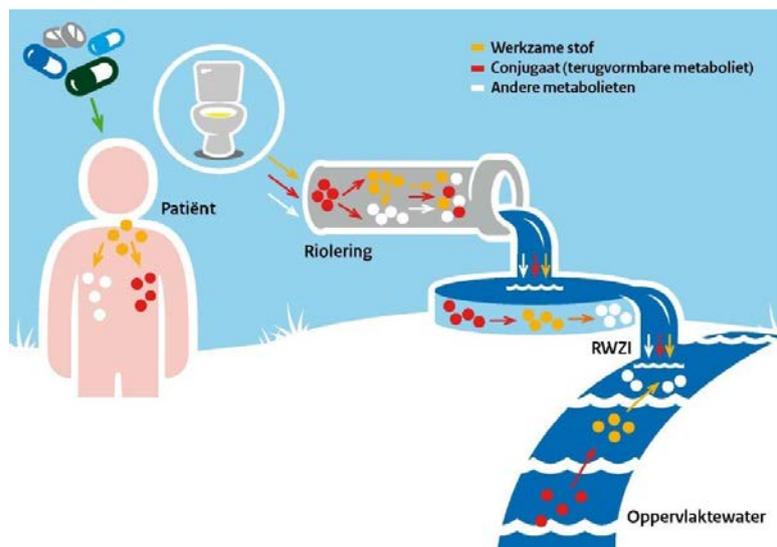
According to the WHO, antimicrobial resistance (AMR) is one of the biggest threats to health and food safety. Resistant microorganisms already cost the lives of 700,000 people a year¹. Research shows that infections with resistant micro-organisms will become one of the most important causes of death worldwide. This is how, in the shadow of COVID-19, another killer of infectious diseases that can no longer be treated is developing. It only takes one resistant micro-organism and medical interventions such as operations are severely hampered because the available antibiotics no longer work. The WHO expects in its report that by 2050, more people will die from AMR than are currently dying from cancer (about 10 million people a year)². The additional global economic damage runs into hundreds of billions of Euros.

Causes of antimicrobial resistance

The main causes of AMR are the (excessive and uncontrolled) use of antibiotics by humans and their use in animals and in agriculture³. The leakage of antibiotic residues particularly from smaller production plants⁴ in countries such as India⁵ and China and the discharge into wastewater of hospitals⁶ and care institutions are also contributing factors. Antibiotics, resistant micro-organisms, and their resistance genes spread invisibly via surface water⁸. In many places, especially in rivers in Asia, the safe concentrations of antibiotics in surface water are greatly exceeded^{9,10} and many people are suffering from the severe consequences of resistant bacteria.

Hospital wastewater: another source of resistant bacteria

Research closer to home shows that hospital wastewater in the Netherlands is a breeding ground for antibiotic-resistant bacteria^{11,12}. A recent STOWA report¹³ shows that the concentration of antibiotic residues in hospital wastewater per hospital bed is significantly higher than the concentration in wastewater from an ordinary 'resident's bed'. This report cites a pilot study which assumes a concentration of antibiotic residues that is 300 times higher. Assuming 40,000 hospital beds in the Netherlands, this would mean that an estimated 40% of antibiotics in wastewater originates from hospitals (see



Source: Dutch National Institute for Health and the Environment (RIVM)

the calculation in textbox). The antibiotics present there can accelerate the emergence of resistant bacteria. This is because bacteria are exposed to concentrations of antibiotics (often leaving the body in an unmetabolized form) high enough to form resistance but not high enough to kill the bacteria.

In contrast to antibiotic use in primary care (the care that anyone can use without a referral such as general practitioner care), hospitals are much more likely to use so-called 'last resort' antibiotics.

These are vital for the recovery of patients who have an infection with multi-resistant bacteria. Of these essential, life-saving drugs, of which there are relatively few of these¹⁴, a significant proportion ends up in hospital wastewater. Chances are that bacteria will subsequently develop there, which then become resistant to these 'last resort' antibiotics.

The impact of hospital beds?

In the STOWA report mentioned above, a pilot study among several hospitals is mentioned in which the number of antibiotic residues in the wastewater per hospital bed turned out to be at least 300 times as high as the concentration in wastewater from an ordinary 'resident's bed'. Assuming 40,000 hospital beds in the Netherlands, this would mean $300 \times 40,000 = 12,000,000$ units of 'resident beds'. This means that the hospitals would discharge antibiotics for 12,000,000 'resident beds'. This is 12 million divided by (12 million + 17 million inhabitants) = 41% of the antibiotics used for human consumption in the Netherlands which would end up in hospital wastewater. The research results are too limited to justify such an extrapolation. However, it does indicate that further research into the impact of hospitals and healthcare institutions is warranted.

Simply removing antibiotics is not enough

Resistant bacteria, which arise because of treatment with antibiotics, can pass on their resistance to their progeny and to other bacteria. The latter takes place by the transfer of 'plasmids' containing the relevant resistance genes¹⁵. The current practice in hospitals and care institutions often does not (yet) provide for the disinfection of wastewater and/or removal of these 'freely occurring' plasmids containing resistance genes. This means that resistant bacteria and resistance genes can easily reach sewage treatment plants and surface water via hospital wastewater and spread their resistance there¹⁶. This leads to a (further) increase of the AMR problem.

Preventing the spread of AMR via water requires a three-pronged approach

This three-pronged approach consists of:

1. The best possible removal of antibiotics present in wastewater
2. Disinfecting the treated water (so that at least the pathogenic bacteria are rendered harmless)
3. Removing the plasmids containing the resistance genes.

In other words: we will not prevent AMR if only the antibiotic residues are removed from wastewater. We will have to do more. In addition, the resistance problem also applies to other micro-organisms such as fungi and viruses¹⁷. This means that we will also have to remove other antimicrobial agents (such as antifungals) and, when disinfecting, also remove these other microorganisms. This three-pronged approach is new and has positive consequences for the emission of other medicine residues into surface water as well.

Treatment at source goes hand in hand with end-of-pipe sewage treatment

The removal of antibiotic and medicine residues, resistance genes and (resistant) bacteria both 'at source' (in wastewater from hospitals, care institutions and production sites) as well as through end-of-pipe solutions in sewage treatment plants is crucial. At the source, the concentrations of medicine residues are high compared to the much lower concentrations in wastewater treatment plants. This applies in particular to antibiotics, including the aforementioned 'last resort' antibiotics. Removal at source is a very effective way of preventing antibiotic-resistant bacteria from developing and spreading. This also applies to the production of antibiotics. It is very important that adequate purification takes place at all production sites in countries such as India and China. Not only is this important for the people living over there, but also for everyone else.

In addition, the purification of hospital wastewater serves an important secondary purpose: if treatment is carried out in a sustainable manner, adverse effects of resistance and environmental effects do not get in the way of prescribing and doctors can focus on providing the best care. In the meantime, various hospitals have implemented extra purification steps at the source! This is an encouraging start!

Further 'end-of-pipe' investments in sewage treatment plants are urgently needed because of the large contribution of medicine residues originating from households. However, when it comes to antibiotics, end-of-pipe purification has already allowed many new resistant bacteria to emerge.

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Additional purification techniques (the so-called “fourth treatment stage”) must therefore also be able to remove resistance genes. The post-treatment of treated sewage water currently has the justified attention of many knowledge institutions and water boards in the Netherlands.

Pharmaceutical residues in the environment

Medicines are an indispensable part of our everyday lives and provide valuable and essential contributions to people’s quality of life. They ensure that chronic diseases become bearable or can even be cured. Think, for example, of insulin for diabetic patients. Many other diseases can only be treated using medicines, such as antibiotics or medication against tumours. At the moment, the probability to survive breast, prostate- or skin cancer is, thanks to medicines, around 90%¹⁸. With medicines, diseases can be prevented, as is the case with vaccinations, or, in the case of cardiovascular diseases, the risks of developing them can be greatly reduced.

However, pharmaceutical residue spills, especially through urine and excrement (90-95%), into sewers and subsequently into the surface water of ditches and rivers. Calculations by the National Institute for Health and the Environment (RIVM) demonstrate that, even after the purification process, at least 190.000 kilos of medicine are discharged into Dutch waters on an annual basis¹⁹. This is separate from the contamination of other emerging chemical substances. It is likely that the reported quantities are higher, because the distribution of medicine in hospitals and via ‘over-the-counter’ sales in drugstores were not included in the calculations, nor was the ‘re-formation’ of live components from drug leftovers (50-500 tons per year). Such medicine residues and other micro-pollutants pose a risk to the ecosystem and aquatic life. To maintain the quality of our drinking water, increasingly more effort is needed. Even though pharmaceutical companies consider their product’s removability from water at an early stage of the manufacturing process, more and more sophisticated techniques will be necessary to bring the quality of drinking water to the standards currently in place. This has to do with the fact that medicine must be difficult to disintegrate to be effective in the body²⁰. This is not just the case for antibiotics.

Specially outside of Europe

On average, high-income countries treat 70% of the urban and industrial wastewater they produce²¹. In upper middle-income countries this number is only 38%, and in lower middle-income countries the percentage of treated wastewater drops to 28%. In low-income countries, only 8% of the wastewater is treated in

some form or other. It is estimated that globally more than 80% of all wastewaters is disposed of without any treatment at all.

Limited use of knowledge and technology

Various European companies already have invested in water purification technology that can be applied “at the source” and “end of the pipe”. Multiple water boards in Europe currently explore the use thereof. Knowledge institutions are obtaining new knowledge, developing sustainable technological solutions for the purification of wastewater²². This knowledge, among other things, must be increasingly focused on the removal of antimicrobial agents, rendering micro-organisms harmless, and eliminating genetical material such as plasmids.

Examples of these types of solutions range from new and decentralised, small-scale, biological treatment concepts to physical/chemical treatment technologies such as treatment with UV, ozone, and/or peroxides, and absorption processes. This knowledge and such technologies are already successfully applied (and sometimes mandatory) in other sectors, for instance, in the Dutch greenhouse horticulture sector²². In the Dutch healthcare sector for instance, these technologies are yet insufficiently and ineffectively being applied. There are several reasons for this:

- Most hospitals and healthcare institutions are unaware of the AMR problem in water.
- Hospitals and healthcare institutions are unaware of the available technologies that solve the problem.
- Legislation regarding the discharge of wastewater from hospitals and healthcare facilities insufficiently targets the prevention of AMR or the limitation of the ecological effects caused by medical residues²³.
- The treatment of wastewater is mainly focused on purification at central sewage treatment plants and rarely on treatment at the source (in hospitals and care institutions).
- The approach to the problem of medicine residues is generally focused on quantities and “loads” (quantities of medicine residues discharged per day) and not on substance-specific (health) effects (such as AMR) nor at ecological impact. As a result, various harmful and/or perilous substances, such as specific antibiotics that are used in hospitals, are missed.
- There are no guidelines or structural agreements as to who pays the costs for purification other than the purification expenditures that are charged by the water board (in which medicine residue is not a tax base).

In practice, this means that there is currently too little intervention at the source.

The question: who pays (and oversees the discussion)?

If the polluter pays, then who is the polluter?

In the Netherlands, the 'polluter pays' concept has been the accepted basis to recover the costs of water treatment from the polluter since the introduction of the Dutch Act on Pollution of Surface Waters in 1970. In the case of contamination with plasmids, antibiotics, and medical residue, finding out who the polluter is, is a key question in the discussion. Instead, we should collectively search for the most sustainable and effective solutions. The question of who the polluter is and whether they can be held accountable for the costs of treatment, is not easy to answer. Are the polluters:

- The patients, who depend on medicine for their treatment and whose medicine residue winds up in the toilet, with their health insurance usually bearing the costs of the medicine?
- The hospitals, which are bound by agreements to a growth of 0% and therefore can only make savings?
- The wholesalers, distributors and (hospital) pharmacists, who distribute the medicine and are bound by dispensing fees?
- The pharmaceutical companies, who produce the medicine and are bound by the Dutch purchasing system on lowest price (80% of the volume of medicine residues in surface waters are purchased at rock-bottom prices)²⁴?
- The water boards, which must make extra efforts to implement additional steps to the treatment procedure?

Or is it society, as we heavily rely on clean drinking water and the efficacy of these antibiotics? The costs for removing antibiotics

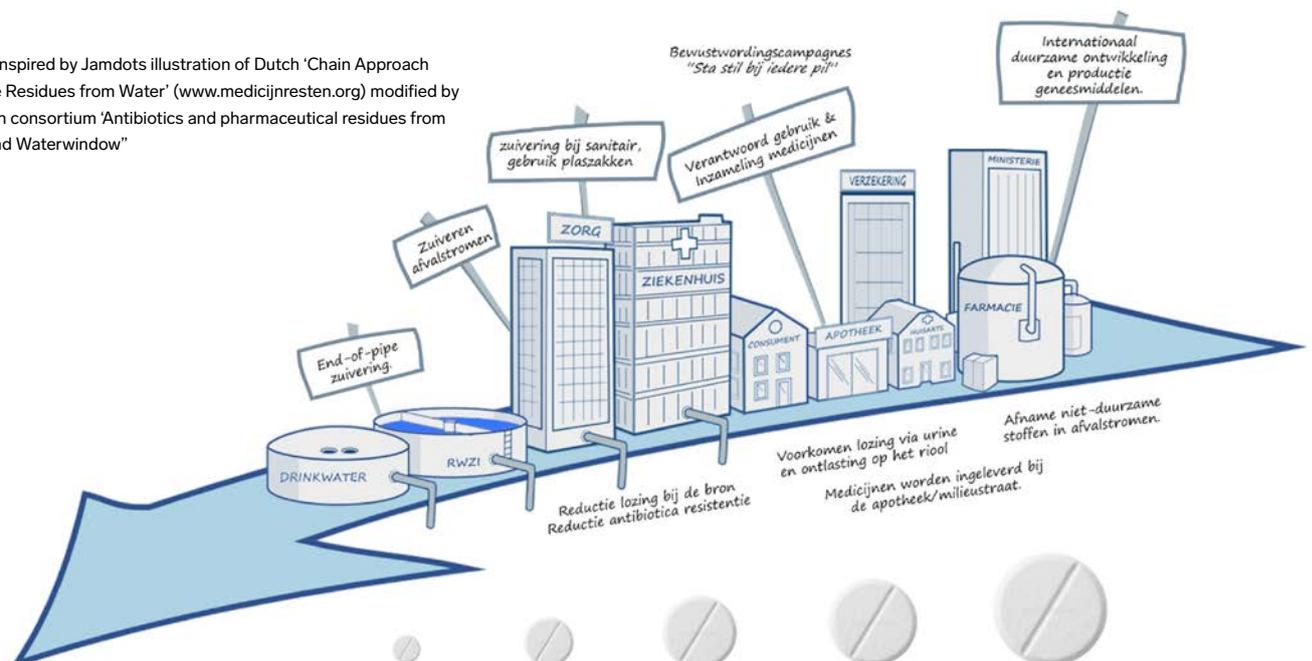
and medicine residues are not factored into the costs of healthcare, the prices of medicine, the costs of drinking water, or by any other means.

By providing a better insight into which (affordable) solutions are available for the purification of antibiotic and other medical residues from wastewater and by investing in advanced development and upscaling, the costs will become lower, and, in the long term, we will prevent considerable economic damage that AMR and medical residues can cause to humans and the aquatic environment.

Interplay between the water, health care, and pharmaceutical sector is both crucial and promising

The growing problem of bacterial resistance and the contamination of waste and surface water through antibiotics and other medical residues demands a targeted joint approach. This is the core of a new Dutch chain-approach 'Chain Approach Medicine Residues from Water'²⁵. The national government (specifically the Ministry of Infrastructure and Water Management and the Ministry of Health, Welfare, and Sport) closely work together with parties from the water sector, the healthcare and the pharmaceutical sector. In the meantime, in the context of 'Acceleration table of the Delta Approach Freshwater Quality', the first administrative agreements have been formulated for the period 2021-2023²⁶.

Source: Inspired by Jamdots illustration of Dutch 'Chain Approach Medicine Residues from Water' (www.medicijnresten.org) modified by the Dutch consortium 'Antibiotics and pharmaceutical residues from water' and Waterwindow"



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The starting point is and remains the fact that medicines should stay accessible to everyone who needs them.

Removing pharmaceutical residue from the water is one of the four pillars of the Green Deal for Sustainable Care²⁷ in The Netherlands. All parties involved have agreed to take a pragmatic approach. This means that waiting is no longer an option, instead, wherever possible, they act now.

The sooner we act, the better

Even better than removing antibiotics and other pharmaceutical residues 'at the source' is to prevent them from ending up in wastewater in the first place. At an international level, pharmaceutical companies are working hard to include environmental aspects at an early stage in the development phase of new medicines. Many countries have set an example for the rest of the world when it comes to responsible prescribing²⁸. However, there is still room for improvement when it comes to patient's lifestyles and appropriate drug issuing policies which can prevent further wastage^{29 30}. For instance, the precise prescribing policy adopted by pharmacists and doctors in the municipality of Asten (NL) has ensured that 20% fewer medicines are dispensed and therefore 20% less drug residues end up in the surface water. For example, instead of a whole box of painkillers (30 units) being dispensed, only 10 units are given to evaluate the effectiveness of the treatment. After responsible prescribing, the next step is to implement smart sanitary solutions. These include: 1) the use of urine collection bags for bedridden hospital patients who are treated with specific medication, which makes it possible to render the bag's contents harmless, 2) the inclusion of a purification step in the hospital's sanitary facilities, and 3) the disintegration of antibiotics and pharmaceutical residues at pharmacies/environmental collection points (instead of flushing them down the toilet).

We should also work on the redistribution of leftover antibiotics and medicine (after their quality has been ensured by a pharmacist). Other smart solutions are at our fingertips.

Raising awareness about the dangers of AMR and its ecological effects and sharing knowledge about available solutions among all parties involved is and remains important. For example, this is done during an annual nationwide collection week of unused medicines in the "Week of Our Water", in October³¹.

In addition to cooperation, there is also a need for teamwork

Cooperation between hospitals and companies from the water and pharmaceutical sector is crucial to prevent the emergence of antibiotic resistance and the adverse ecological effects caused by the discharge of antibiotic and medical residue in the coming decades. In addition, all parties involved need to work together:

- The pharmaceutical sector, which contributes to the aforementioned solutions at the source to prevent antibiotic and medical residues from ending up in wastewater (clean production) and contributes to the sharing of knowledge about new and existing substances. The pharmaceutical companies that are already considering the removability of antibiotic and medical residue from water and decontaminate their own wastewater. Furthermore, these companies can contribute to raising awareness and the development of technology through water stewardship programs, the AMR Industry Alliance, and the Pharmaceutical Supply Chain Initiative (PSCI).
- General practitioners, dentists, veterinarians, and pharmacists who ensure responsible use of medicine by targeted prescription and supervise appropriate usage, dispensing, collection, and responsible disposal together with their respective municipalities.
- Hospitals and other care institutions, which work together on practical research and demonstration projects of new technology and smart sanitary applications.
- The water sector: 1) Water boards that apply knowledge, 2) knowledge institutions that develop new, sustainable, and more affordable technology for the measurement and removal of antibiotic and medical residue, rendering micro-organisms harmless and removing resistant genes (both 'at the source' and 'end of pipe'), and 3) the industry which contributes to the valorization and commercialization of this technology.
- Government institutions and health insurers which establish appropriate preconditions, such as, a dispensing policy, legislation, and regulation, supervises compliance, and invests in new, affordable, and sustainable technology.
- Other national and international governments that follow the example of the Netherlands.

Through investments, solutions for AMR will become more affordable. This allows for appealing financial opportunities, because the global demand for purification technology will steadily increase.

A good example is greenhouse horticulture

With thousands of companies, 10,000 hectares of cultivated land, and many high-quality crops, the Dutch greenhouse horticulture sector is a major motor of the Dutch economy. Due to complications concerning the emission of nutrients and high concentrations of crop protection products in the surface water in and around greenhouse areas, the sector itself took the initiative to work on solutions in 2012. In various platforms and development projects, such as 'the Sustainable Greenhouse Horticulture Platform' and the innovation program 'Greenhouse Horticulture Waterproof', the greenhouse horticulture sector and government authorities are now working together on policy and technological solutions in the field of greenhouse horticulture and sustainability. Their main point of focus is water. Together with the Dutch government, the sector has agreed on a long-term goal of virtually zero emissions in 2027. As of 1 January 2018, the obligation to purify the companies' wastewater of crop protection agents prior to discharge had to be met. To do this, small-scale purification systems are used that remove at least 95% of the active substances that are present in the wastewater, including many organic compounds [Helpdesk Water, 2021].

Theo Cuijpers, involved in both issues and active in the Hoogheemraadschap Schieland en de Krimpenerwaard: "The cooperation between greenhouse owners, chain partners, scientists, and government bodies has proved to be of great importance in limiting the discharge of harmful substances into the environment. On the one hand, the cooperation has led to awareness and changes in the day-to-day operations of greenhouse horticulture. On the other hand, the development of new technological solutions has been pursued, such as affordable and certified water purification techniques. In my opinion, this approach can perfectly be applied in hospitals and nursing homes to deal with the discharge of antibiotics and other drug residues." For more information:

<https://www.glastuinbouwwaterproof.nl>

<https://www.helpdeskwater.nl/onderwerpen/emissiebeheer/agrarisch/glastuinbouw>.

The most effective approach is to focus on AMR

The 'Dutch Consortium on Antibiotic and Medicinal Residues from Water'³² works in line with the ambitions of the above-mentioned chain approach and other public-private initiatives (such as AMR Global, Health Holland, LSH). The Consortium, which is open to everybody, focuses on reducing AMR (inside and outside the Netherlands) and consists of a 'Coalition of the Doing' in which 18 public and private organizations from the water, healthcare, and pharmaceutical sectors are currently affiliated with. The Consortium brings together knowledge of, and experience with solutions for AMR. In addition, the Consortium investigates new solutions for various local and central applications.

The Consortium is developing into an international network organization

Multiple initiatives are taking place around the world to tackle AMR. It is of great importance that results from cross-sector collaboration are used in an international context. This will create major opportunities for the exportation of water technology. This is good for humankind, the environment, and for the innovative power of economies. Because AMR and the environmental effects of medical residues do not respect national borders.

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Dutch partners



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