



# World Health Organization

## **Antibiotic-resistant priority pathogens list**

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### **Speaker key:**

MO	Moderator (Fadéla Chaib)
MK	Marie-Paule Kieny
HB	Helen Branswell
NM	Nicola Magrini
DMK	Deborah McKenzie
CO	Christiane Oelrich
ET	Evelina Tacconelli
GV	Gonzalo Viña
CP	Carmen Pessoa Da Silva
DMN	Donald McNeil

MO Good morning, good afternoon. I am Fadéla Chaib, Communication Officer at WHO. I will moderate this press conference from Geneva. I want to welcome journalists on the phone. The subject of today's press briefing is the publication by WHO of its first ever list of bacteria for which new antibiotics are urgently needed. It's a catalogue of 12 families of bacteria that pose the greatest threat to human health.

Spokesperson for today's briefing include Dr Marie-Paule Kieny, who is WHO Assistant Director-General for Health Systems and Innovation, joining us by phone from Oslo. With Dr Kieny are two experts who are present here with me who have been leading several areas of work on this important topic and available for your questions; first Dr Nicola Magrini. He's Scientist, Department of Innovation, Access and Use of Essential Medicines, WHO; and Dr Carmem Pessoa Da Silva, Co-ordinator a.i., Antimicrobial Resistance, WHO.

We will open the press conference with a short statement from Dr Kieny and then we will open the floor for questions to Dr Kieny or other experts available. To ask a question, I remind you, you need to dial 01 on your telephone keypad. Dr Kieny, please, you have the floor.

MK Thanks a lot, Fadéla. Dear media colleagues, the news today is that we are publishing a list of the top 20 drug-resistant bacteria that require prompt action from the scientific research community to develop new antibiotics to treat them. They have been identified by a group of international experts led by WHO and the University of Tübingen in Germany, according to the best evidence available and strict criteria. You will find the full list of those criteria in the press release but to sum up, the four key things we looked at were: first, the

level of resistance to existing treatment; second, mortality rates; third, prevalence in the community; and finally fourth, burden on the health system.

This is one of several WHO workstreams to address antimicrobial resistance, which must be tackled from several angles and in a comprehensive way. This new global list clearly sets three priorities for research and development of new antibiotics—critical, high or medium—to convey the level of urgency for the antibiotics needed.

I must highlight at this point that *Mycobacterium tuberculosis*—the bacteria responsible for tuberculosis—was not included in this exercise, as there is already consensus that tuberculosis is the most important priority for R&D for new antibiotics.

Now, the critical priority category includes multi-resistant *Acinetobacter*, *Pseudomonas* and *Enterobacteriaceae*. This is truly urgent. These bacteria are responsible for severe infections and high mortality rates, mostly in hospitalized patients, transplant recipients, those receiving chemotherapy, or patients in intensive care units. While these bacteria are not widespread and do not generally affect healthy individuals, the burden for patients and society is now alarming and new, effective therapies are imperative.

The high-priority category includes bacteria that can occur in healthy individuals, such as gonorrhoea, *Salmonella*, *Campylobacter* and *Helicobacter pylori*. These infections, although not associated with significant mortality, have a dramatic health and economic impact on communities and in particular in low-income countries. Plans should be in place to integrate new antibiotics against these pathogens in the R&D pipeline in the near future.

The third priority which we called medium, includes bacteria that represent a threat due to increasing resistance but still have some effective antibiotic options available.

So why do we need such a list? Well, until about 30 years ago, the world was seeing tens of new antibiotics being approved and coming to market but today, just when resistance to antibiotics is reaching alarming proportions, the pipeline is practically dry. The problem is clearly one of a scientific nature as new antibiotics are becoming more difficult to discover, but no market incentive is also an issue. Antibiotics are generally used for the short term, unlike therapies for chronic diseases, which bring in much higher returns on investment.

There are also market distortions to consider. Indeed, rather than seeking to maximize sales of a new antibiotic—which would mean it would lose effectiveness earlier due to resistance—there is a need for stewardship to reduce the use of antibiotics and slow the inevitable development of resistance. This is why the global list is important; it's not meant to scare people about new superbugs. It is intended to signal to the scientific community and the pharmaceutical industry the areas they should focus on to address urgent public health threats. For example, the list will provide guidance to new R&D initiatives such as the WHO DNDi Global Antibiotic R&D Partnership, or GARDP, which is engaging in not-for-profit development of new antibiotics.

The list is also meant to spur governments to put in place policies and incentives to promote basic research and advance R&D by both publicly-funded agency and the private sector investing in new antibiotic discovery. What could some of the incentives look like? Well, Jim O'Neill, chair of the UK antimicrobial resistance commission, for example, has suggested that companies that develop new antibiotics should receive market entry rewards of US\$1 billion

so they recoup the cost of R&D as soon as the drug is launched. The money would be paid on condition that companies are responsible for stewardship, ensuring antibiotics are available when needed but not overused so they lose their effect. This would delink profit from the volume of sales and make development financially attractive.

Jim has also proposed a US\$2 billion global innovation fund to kick-start a new cycle of early-stage research and generate inputs for pharma industry pipelines. China and the UK have already pledged US\$72 million to the fund. So, with this list, we are also asking governments to commit funds to R&D to address antibiotic resistance now in order to reduce the amount of resources that they will need to spend later when resistance to antibiotics develops into an even bigger crisis.

My final message is this; this list is truly an example of society or the public health community requesting that R&D responds to an urgent public health need. Governments and industry must work very closely on this if we are to find new weapons to fight growing antimicrobial resistance. Thanks a lot.

MO Thank you, Dr Kieny. We will now take the first question; just reminding you of the embargo that is lifted at 3:00pm GMT, at the end of this press conference; thank you. Helen.

HB Hi, thanks very much for taking my question. Can you hear me?

MO Yes, we can.

HB Thank you. I was just wanting to ask, is there any reason to believe that the research that's being done to develop new antibiotics is not focusing on these priority pathogens? I mean, some of these issues have been, you know, well-enunciated in the past. I would think that these would be the targets that pharma would be working on.

MK Sorry. Fadéla, can you indicate who should respond to this question? Yes, so this is Marie-Paule Kieny. Yes, of course, you know, there is a lot of investment, a lot. There is growing investment now and new renewal of interest in development of antibiotics. But what we are seeing here is that we may also have come out of the development of very broad antibiotics which are used, can be used against a whole range of bacteria and we may now have to focus on antibiotics which would be specific for a much smaller range of bacteria.

And so in this list we want to make the point that if it is possible to develop antibiotics which target specifically and exclusively some of the critical pathogens, this would also be welcome.

MO Thank you, Dr Kieny. Other comments from our experts here in Geneva? Yes, Nicola? Nicola Magrini would like to add a few words.

NM Well, I would like to add a comment on the fact that currently the pipeline in the last ten years has been richer in research on gram-positive agents that probably have - well, on one side are less difficult to tackle somehow, they generate less resistance less easily, but also can generate wider market. So the idea to specifically try to shape the agenda towards the most severe, though with small market, gram-negative for several infection restricted to the hospital is a strong message, for which we should try to find new incentives and new mechanisms to sustain the investment that the industry could be making in the near future.

MO Thank you.

HB Thank you.

MO We will take a second question from Deborah McKenzie. Deborah, please go ahead.

DMK Hello, thanks very much. I'm wondering about - I mean, you've rightly stressed the very lethal kinds of infections that these agents can create in hospitals and healthcare settings. But I'm wondering about the very common bacteria found, bacterial infections, especially gram-negative infections and we particularly have urinary tract infections here that are increasingly resistant to the available antibiotics and in fact in some cases are becoming untreatable.

Presumably that must - although the mortality isn't high but the number of people who are infected must make that of equivalent concern, although perhaps not according to the criteria you've used here. I was wondering if you'd sort of thought in terms of the numbers of people affected versus severity.

MO Thank you. Marie-Paule, do you want to take this question? Or also Nicola is ready to help.

MK I think that it would be good if Nicola could highlight the criteria because indeed what is mentioned is part of the criteria used for this exercise. Nicola, over to you.

NM So yes, in the third-listed or third-ranked family, *Enterobacteriaceae*, is included *Escherichia coli*, that can be responsible of severe infection in catheter-associated infections so yes, that is highlighted. That could be also a potential market; it's not a rare infection but still it's not at all an easy target and it was just highlighting that research has spontaneously directed itself toward gram-positive.

MO Thank you, Nicola. We will go now to Christiane Oelrich from DPA, based here in Geneva. Christiane, over to you.

CO Thank you very much for taking my questions. This is a layman's question because we are writing for the general market. How many people are affected, is, can you give us a rough estimate, how many people would benefit from antibiotics being developed for these 12 families? And can you elaborate a little bit on the problem in nursing homes? Because that seems to be affecting a vastly bigger number of people than the ones you mentioned, transplant recipients and chemotherapy patients. Thank you.

MO Who wants to take this question? Nicola?

NM I think also Evelina Tacconelli is on the phone. She could be. However, in the preparation of the evidence summary for our experts, prevalence and incidence of each diseases were quantified to contribute to the ranking. Some of these infections can be accounting for hundreds of thousands of infection worldwide. We didn't go for such an estimate right now. It will be part of the final report that will be a very rich report. Today we publish only an abstract plus the list in order to contribute to the G20 discussion in the forthcoming months. The full report will be ready by June and some of these numbers will be

available, as they've been in previous reports, and certainly the burden of the disease is there but for the critical ones certainly it's the severity and high mortality rate that drove their ranking.

MO Okay. Now maybe to add some comments we have joining by phone Professor Evelina Tacconelli. She's the head of the division of infectious diseases at the University of Tübingen in Germany and also she's a major contributor to the development of this list. She's on the phone. Professor, are you hearing us?

ET Yes, I'm here, yes.

MO Thank you.

ET Maybe I can just have a very short comment on the last two questions that were making a very important point. For us it was very important not to underestimate the burden of this disease in the community because I totally agree that the burden of healthcare-associated infection is important, but the urinary tract infection for example in women and in the elderly population are having an amazing burden in our community, as well as nursing homes.

So we try to have this information included in our criteria so we have two specific criteria; having specific focus on nursing home transmissibility as well as for infection that do not have a mortality, high mortality at least, as urinary tract infection but do have high burden in the community. So the system is calibrated to give importance also to this infection as well.

MO Thank you, Professor. We'll go now to another question from Mr Viña, Financial Times.

GV Hi, good afternoon. Just a quick question on what drug companies should be doing; you talked about incentives earlier on and market distortions. Is it down to the companies or is it down to public health systems or should they be working together. Could you outline what the kind of programme of work should look like?

And the second question; how urgent is this work? Could you give us some sort of sense of what happens if we don't have this work done within the next, you know, one, two, three, five years? Those two points please.

MO Dr Kieny?

MK I can take this one. So what is important is that the public health authorities are clear with the pharmaceutical industry about what is needed, what are the public health needs and this is why the list of priority bacteria is important so that they (industry) know what are the expectations of public health officials. So after this prioritization exercise there must be collaboration with the private sector. Indeed - and this was mentioned several times - there is a market failure. If we want to develop new antibiotics it's not to use them *larga manu* / (Latin word- that means without discrimination- please note this is an addition from the reviewer) like has been the case for the previous ones so that the resistance grows so quickly that in very few number of years they are of no use any more.

So we need first, as I said, the help of the public sector and the public health officials to identify the targets and then we need to collaborate with the industry to find ways of doing research which makes it that the research is not something that the industry has to pay for alone without a hope of being compensated at the right level. So this is where the incentives and the work of the UK—and in particular of Jim O'Neill—is important, in the sense that it puts on the table new models that could help the industry to take interest in this development and invest therefore in R&D, without at the end needing to recoup their investment by volume sales. So this is a collaboration that we need to have between the public and the private sector.

Now, in terms of urgency, as you know, it's not because you decide that you should discover and develop new antibiotics today that they will be tested and available for use tomorrow so this is why it is very important to start now, as quickly as possible, in order to have down the line in three, five, ten years, to have the antibiotics that we need.

GV Okay.

MO Thank you, Dr Kieny. Just reminding journalists willing to ask a question, they should type 01 on their telephone keypad. Now we will take Deborah McKenzie, who has a follow-up question. Up to you, Deborah.

DMK Thanks very much, sorry to bother you again.

MO No.

DMK I was intrigued by Dr Magrini's mention of a lot of work on new agents apparently being directed towards gram-positive infections. Could he tell me or could one of you tell me why that's happening and what in particular are the infections that are receiving the attention?

MO Dr Magrini?

NM In my view it's mostly linked to look for similar antibiotics or inhibitors for Beta-lactamase where more work has been done toward finding new combinations or new chemical structures that could tackle this. So there was a stream of work directed towards these gram-positive pathogen that was, let's say, streamlined and probably more easy to undertake, also under the perspective that these could be larger markets.

As you know, antibiotics are often approved on a small number of indications or studied mostly on simple, often soft tissue infections with non-inferiority trials and then used in a wider range of infections or when needed because of sensitivity testing. So that was probably more straightforward and researchers know that on gram-negative, that the sources or more easy sources of difficult-to-combat resistance, it has always been more difficult to find new antibiotics. So the working group was quite happy of the final result, indicating gram-negative as the top priority. This should foster and support much more basic research science too so this is an invitation also to public agencies to fund more research work and bench work on gram-negative in general because the discovery of an antibiotic is truly a complex task and not at all something simple and straightforward. So we have to go back to basic research and then think about quicker development.

DMK Thank you.

MO Thank you. We will now ask Professor Evelina Tacconelli if she has something to add.

ET I think Nicola already gave a comprehensive answer. Maybe I can just add from clinical point of view that these clinical trials for multidrug-resistant gram-negative are very difficult and expensive to do, more than for gram-positive because when we talk about gram-negative we need to cover multiple pathogens and not just one or two, as the case of gram-positive, with different indication.

They cause a skin infection more readily as gram-positive and obviously a clinical trial on skin infection is very much easier to make as for example unventilated-associated pneumonia for the gram-negative. The diagnosis is very much more complex for gram-negative than for gram-positive and there is a lot of cross-resistance among antibiotic classes that we do not see for the gram-positive.

So it's very much an economic and scientific issue to keep a trial on this type of pathogen until the end and to build it up, and that is one of the reasons why until now in the last year we really had a very few trials covering multidrug-resistant gram-negative bacteria.

MO Thank you, Professor. We will take now another question from Helen Branswell. Helen.

HB Hi, thank you. I need to ask a stupid question. I need some help explaining to lay readers the difference between gram-negative and gram-positive and I know that it's about staining but that doesn't really tell anybody who's not a microbiologist very much. So could you please give me a sense of how to describe gram-negative bacteria, you know, what families of bacteria typically they encompass; how can I differentiate between these two, please?

MO Professor Tacconelli, maybe this is a question perfect for you.

ET Okay. I'll try to do it in one second. I would say that there are two families, from many aspects very similar, but the gram-positive that could be dangerous—and I refer here to our list—for the health are mainly colonising the nose and, let's say, the skin of healthy individuals. When we talk about gram-negative, we find this gram-negative more frequently in the abdomen of the individuals, in the stool, colonizing the intestine of the healthy individuals.

So this is, I would say, the most important issue, and for this reason they cause different patterns of disease. At the moment, the gram-negative, being in the intestinal reservoir, they can give very severe sepsis and very severe urinary tract infection, in particular in elderly population or in immunocompromised and in hospitalized patients. I don't know if this answer your question.

HB Yes, thank you.

MO Thank you. We will have also so comment from Dr Carmem Pessoa Da Silva from WHO. Carmem?

CP Yes, of course, Evelina has already provided a very, very wide and comprehensive explanation. I'll just like to remind everyone, when we talk about gram-negative, we are also referring to bacteria that cause serious infections in hospitals and that are not necessarily colonizing the intestines, like Evelina mentioned, but may be contaminating equipment and leading to surgical site infections; also respiratory infections associated with support, ventilatory support.

And this has been a major challenge for modern medicine because these bacteria; they are really spreading very frequently in healthcare facilities and we also need to address them.

MO Thank you, Dr Pessoa Da Silva. Now we will go to Don McNeil, New York Times. Don?

DMN Hi, thank you. Does the WHO have an overall world estimate of how many people die of drug-resistant infections each year? I know the United States estimates about 23,000; the European Union just estimated last week about 25,000; but I'm trying to find a world, overall world estimate, even if it's a couple of years old.

And just coincidentally, do you realize how messed-up your website is? I've been trying to call up the simple page, antibiotic-resistant infection, you know, and the connection constantly breaks and it's been happening for a week and if I'm having trouble from New York, there must be people all over the world with worse internet connections that can't get any WHO information.

So I'm basically asking, do you have an overall world number for deaths?

MK This would be a question for Carmem.

MO For Carmem.

CP Thank you very much for your question. The short answer is we do not have right now an accurate response to this. Now, we are working on, to improve the capacity to respond to this. One of the reasons for why we do not have the overall mortality due to antimicrobial resistance is because we do not have in the international codes of disease any indication that the cause of death was due to antimicrobial resistance.

So exactly to address this issue, the international code of disease is being revised to try then to include the code in a way that in the future we'll be able to measure the mortality due to AMR so this is one aspect.

But I have to say also that although this is not right now available, in addition to the international code of disease, the WHO has launched the Global AMR Surveillance System, exactly also to build the capacity to globally measure the magnitude of AMR on human population.

MO Thank you. Don, thank you for your comment on the website. We will be looking at this issue later on.

DMN It needs attention. Maybe someone at the Gates Foundation who has connections to Microsoft can help you.



MO We will look at this. We have also very good colleagues dealing with web issues. I think we have no other question for now. If we have any other comments from the experts... if you want to add something...

MK If I can add something actually, there is, I would like to highlight the momentum that there is right now on understanding the threat of antimicrobial resistance and also on trying to do something in order to address the problem now. So this is excellent; it must be done by several angles, if I may say. It must be done also by having a One Health approach, so this is why WHO is working very, very closely with OIE for the animal health and FAO for agriculture. And it is only working together, across sectors—and across the public and private sector—that we will be able to resolve the issue.

Resolving the issue has a mix of very different intervention. Of course you need R&D for new antibiotics and for this it is important to identify which are the bacteria which are the most important and this is where our priority list is the first step forward. But we need also to look at how best to have stewardship of these antibiotics, to avoid that they are overused and misused and many other elements that are needed, as was highlighted in the AMR Global Action Plan that was presented and endorsed in the UN.

MO Thank you, Dr Kieny. I can see that we have a follow-up from Christiane Oelrich from DPA. Christiane.

CO Yes, hello. I will also try again on the numbers because this is what all my clients are going to ask me. I understand that you cannot have, you cannot know how many people die of this resistance but do you have estimates or do you think that the estimates that my colleague from the New York Times mentioned are accurate or are somewhere in the right ballpark?

And my second question from before was what is the situation in nursing homes? Why is there a particular problem, and what is that particular problem?

MO Okay, thank you. Carmem, do you want to take the first question on numbers?

CP Well, the first question on numbers; as I mentioned, this is a work in progress, but what we can say in terms of numbers right now is that we have demonstrated that the infections caused by antimicrobial-resistant pathogens, they increase the risk of death by two to three times and to some of the priority pathogens that are listed here, particularly in the priority one.

So, the total number of affected people we do not have, but we do know for sure that there is a significant increase in the number—the risk of death—if the person is affected by a resistant pathogen.

MO Thank you, Dr Pessoa Da Silva. Maybe Professor Evelina Tacconelli would like to respond to the second part of the question about the nursing homes and it will be the last question for this session. Thank you.

ET You're welcome. So as I said before, nursing homes are really an important setting, together with rehabilitation centres and every type of healthcare-associated facility—not only

hospital—and the reason for this is because in the nursing home there is a lot of uncontrolled usage of antibiotics, because unfortunately there is not always a doctor that is present in the nursing home, so when the elderly have fever it would be very difficult to make immediately a diagnosis.

And so the usage of antibiotics is really not always driven by needs of the patients, so the elderly are usually immunocompromised by definition and they have a high risk of infection, in particular urinary tract infection, that could be also sepsis with a urinary origin, and it's very difficult to have infection control within a nursing home. So if there is one patient that will be colonized with an ESBL in the urine, or one that would be incontinent, it's very difficult to control the spread of these microorganisms within the structure.

And just a very short comment about numbers; so I know media, they love numbers, but as a scientist I really have to say that in this case it's very dangerous to keep trusting all the estimations. So the estimations are needed to tell us where we should focus our research, but I think we know that we have mortality of up to 60% of patients for severe infection, with antibiotic-resistant infection. We know that ESBL is up to 70% in many countries for urinary tract infection, and I think this is enough, even if we don't know exactly how many, but we are talking about millions of people affected.

MO Thank you, Professor. Any last...?

MK Fadéla, if you would allow just me a comment about the difficulty of having exact figures about mortality. Can I?

MO Yes, please, go ahead.

MK Okay. So if I can make an analogy, you remember a number of years ago when there was so much—still is—but, there was so much mortality from HIV and indeed people dying from HIV were most often dying from also another disease, Kaposi sarcoma, you know, all the diseases associated with HIV. So the difficulty was, at that time, to decide how to attribute death to a disease or another and it has now come to attribution to HIV, but... so for...

If you look at antimicrobial resistance, people dying of antimicrobial resistance die of primarily a bacterial infection and then the resistance is another factor. So what is happening right now is that there is a lot of work to see how antimicrobial resistance, as one of the factors leading to death, can be coded so that it is recorded in the death statistics. So this is, it looks very technical work, but this is to avoid double counting and there is good hope that soon a solution will be found so that you will not have confusion about the cause of death any more.

MO Thank you, Dr Kieny. Thank you for these comments. We have other comments from Dr Magrini. Nicola, please.

NM Yes, two comments; one is when we are planning for an update, and the update is currently planned in a fairly long time frame, three to five years from now, because the trends are not changing so rapidly. However, also again on burden of disease or counting the number of people who could be affected, we had to rely on published studies and the best available evidence is what has been published or made available, so certainly some countries

and some regions of the world are currently under-represented in available studies, meaning that we need to invest in research on resistance at local level more in order to have those data that Dr Pessoa was mentioning, that are needed, but are not there in all countries. That's why a global estimate is something not easy to extrapolate.

MO Thank you, Nicola. I would like to take this opportunity to thank all of you for being with us today; our experts from different parts of the world and also the so many journalists joining us by phone. Just to remind you that in a very short while, we will be sending you the audio file of this press conference and also tomorrow you will get the full transcript of it. Thanks so much and see you. Bye bye.