WHO: How to stop the next Ebola

Ebola and Zika epidemics have caused frenzies of panic and hysteria worldwide – so how do we stop the next one? Well, the World Health Organization's R&D Blueprint action plan could provide the answer. **Dr Marie-Paule Kieny**, Assistant Director-General of WHO, recently spoke to *Research Features* about this, detailing the importance of platform technologies and relentless research preparation.

Following worldwide epidemics of Ebola in 2014 and Zika virus just last year, it has become clear that a contingency plan to combat outbreaks is badly needed.

This is where the experts come in – the World Health Organization and a global collaboration of research institutions around the world. Their solution is one of precise planning, detailed organisation and faultless preparation, to ensure that the one thing they have not had on their side during recent epidemics becomes less of a concern next time around… time.

Saving time is one of the pinnacle components to WHO's Research and Development (R&D) Blueprint action plan against future epidemics. *Research Features* recently spoke to Dr Marie-Paule Kieny, the Assistant Director-General of WHO and the head of the R&D Blueprint team, to discuss how their plan could equip researchers with the tools they need to combat future epidemics.

Hello Dr Kieny! Thank you speaking with us today. What does your role involve as the Assistant Director-General of WHO, and what kind of responsibilities do you have on the R&D Blueprint team?
I am the Assistant Director-General in charge of health systems and innovation, so I don't typically deal with emergencies. However, during the Ebola epidemic, I was appointed the lead for all of WHO's research and development (R&D) work on Ebola, because of my background in R&D and vaccines. I am currently leading the R&D Blueprint team in collaboration with my colleagues responsible for emergencies, particularly in relation to epidemic threats.

Could you tell us a little more about WHO's R&D Blueprint action plan, outlining what it is you are hoping to achieve from it?
The main purpose comes from the lessons learned following the Ebola crisis, to conduct research and development and evaluate new diagnostics, vaccines and medicines. We should not remain unprepared against other infectious diseases which could create similar epidemics. Research needs to be advanced, drugs need to be developed and vaccines need to be prepared during this so-called peace period – the time we have between epidemics. This is so that when an outbreak hits, these medical measures will have been tested and prepared in advance.

Unfortunately, it is difficult to test their true efficacy without an actual outbreak. So for example, in the absence of Ebola, you cannot assess whether an Ebola vaccine is efficacious or not, although you are able to push the research and development until that stage. Once you have data on safety, you have data on immunogenicity, and you can work out the dose to use when an epidemic hits. By preparing beforehand, you can immediately start evaluating efficacy once an epidemic starts, and then, if everything goes well, have an effective tool ready quickly following the outbreak onset.

The other purpose for our R&D Blueprint is to create a framework – an enabling environment – especially in developing countries that are prone to these kinds of epidemic. This is about advancing clinical trials, discussing material transfer agreements and helping these affected countries establish a national committee to review research projects. At the time of an epidemic, you have investigators of all kinds coming from everywhere. Preparing a framework during this peacetime for how investigations should be conducted during an outbreak, helps to create an environment for organised research.

Why was the R&D Blueprint action plan set up in the first place? Did it develop primarily as a result of the Ebola outbreak?
Yes. Following the Ebola outbreak we had an R&D Summit in May 2015 where we were challenged to develop a plan that would ensure these medical counter-measures could be advanced and available for any future epidemics. After this, all discussions and consultations for the R&D Blueprint action plan were undertaken with all kinds of stakeholders and countries, culminating in this collaborative plan. We then presented this at the World Health Assembly to ministers of all 194 countries from the member states of WHO, who welcomed it and requested we implement it as soon as possible.

Which are the key areas that the R&D Blueprint action plan will focus on?
In the action plan we have three main areas. One is about improving coordination and fostering an enabling environment. This is to try to respond to the problem that we had during Ebola, where there was a lot of goodwill, but very poor coordination. Global coordination is not about WHO telling everybody what they need to do. It is about us convening a forum where the different global stakeholders can come together and discuss what they propose to take on and what their proposed role will be during research. There is this mapping of stakeholders and a good understanding of who's doing what, and also the potential to see organisational gaps that need to be filled – it's about building a global coordination mechanism.

In terms of our second approach, this is to accelerate research and development, assessing the epidemic threats that we have discussed already and drawing up a list of priority diseases. For each of these priority diseases, we will then look to develop what is called an R&D Roadmap. This will look at each of the diseases and establish what ▶

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is in the pipeline, what are the gaps, what is known, what is unknown, what needs to been done, and where the gaps are in terms of funding.

Of course the WHO secretariat cannot do that just on its own – the R&D Roadmaps are not about what we will do, it's about what the international community together will do. We have already conducted one R&D Roadmap, showing us what the needs are for the MERS Corona Virus, what information is currently available and what further work needs to be done to standardise operational procedures.

Our third aim for our R&D Blueprint plan is to harmonise regulatory pathways and obtain a general consensus between researchers for the work that needs to be done when outbreaks arise. This is so that, when there is a debate around obtaining clinical trial authorisation, there is a common understanding between cultures.

How often will these roadmaps be produced for each of the priority diseases?
We have ten priority diseases to develop roadmaps for, so I think they should all be produced in two years' time. Of course, the ones that have been developed first will then be revised regularly to take their progress into consideration.

With the Zika virus occurring last year, and the Ebola virus outbreak occurring the year before that, are you worried that there will be another outbreak next year, as these epidemics seem to be happening on a more annual basis?
Yes, but the main difficulty is that you always prepare for the last war, yet the one coming is more of the same. For example, as you say, following on from Ebola we had Zika and Zika is a completely different virus. Not only is it happening in other countries that are more prepared for mounting a public health response, but there is also a big question with Zika, especially in terms of how much it's spreading worldwide. As you may have seen, it's no longer seen as a public health emergency of international concern, but it seems to still be spreading. For the time being we don't know to what extent, so it's difficult to know what we will need to combat Zika in the coming years.

So what will be the next epidemic? That's what is so difficult to know. Will it be one of the priority diseases that we have identified, or will it be something that comes from the animal world that we don't yet know about? This is why creating an enabling research environment to conduct research against completely new and unexpected threats is so crucial.

When Ebola struck, there were no vaccines or any medical teams available at the time, readily prepared for the outbreak. Yet, after WHO intervened, it sped up the process of intervention massively. Is that basically the point of the R&D Blueprint plan, to prevent the time-lag following epidemic onset?
Yes. Of course when we say there were no vaccines or treatments, we simply mean that there were no commercial products available at the time – there had of course been a number of years of work into this disease. However, this research was not for the purpose of preparing a plan against an epidemic. Instead, the Ebola virus was seen by a number of countries as a disease that could be weaponised. Therefore, because of biosecurity concerns, there had been some prototypes which had been worked on in Canada, in the US, and in some other countries but none of them had gone to testing on humans. So when the Ebola outbreak hit, we were lucky that these prototypes existed as they could be immediately used to evaluate the disease further. We weren't so lucky with Zika though, as nobody had ever thought Zika would do anything. When this virus hit, we had nothing prepared – no prototypes, no trials, nothing.

We want to ensure that this doesn't happen again. The aim for our R&D Blueprint plan is to make sure that all of these priority diseases have therapeutic treatments advanced through at least the early stages of evaluation in animals. That way, when an epidemic hits, we will be ready to advance testing in humans.

For other diseases that we may not necessarily know about, the only thing we can do is make sure we have a structure in place. This will ensure the clinical design is appropriate in view of a particular disease's characteristics, transmission and incidence.

A WHO researcher working in the Ebola lab at Donka Hospital, Guinea

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Will the R&D Blueprint plan incorporate educating the public as well or is it more research-focused?
It's more research-focused but will also place high value on communication. One of the tools we are developing is aimed at guiding good community engagement practices, seeing how we engage with communities to help them understand what a disease is, what research is going on, and how they can be part of it.

So you can apply your disease R&D Roadmaps to update them about what's going on before and during an outbreak?
Yes, exactly.

With the reduction of time it takes to release treatments and vaccines once an epidemic hits, is there a risk that the efficiency and success of these treatments will be reduced, because you're releasing them under more rushed circumstances?
Well this is why it needs to be worked on in advance during the global peacetime between epidemics. This will give us more time to look at the safety and the pharmacodynamics, so that we can at least have the basic knowledge in place before intervening in an affected country.

For example, when the Ebola outbreak first hit, we worked primarily on finding a vaccine against it, but by September there had been no clinical trials. This is why there was a need to do parallel trials, in order to feel confident that when you go and start trials in Guinea or Sierra Leone or Liberia you are not hurting people.

During the clinical development of vaccines, there is usually the first phase which involves a few dozen people. Following this, there is the second phase, involving a few hundred people, before the third and final phase, involving a few thousand people. Because of the time pressure on Ebola, we had to start multiple phase one trials at the same time – because single clinical trial centres cannot do 100 people together in parallel but we needed a detailed evaluation as soon as possible. In fact, during the production of the Merck vaccine in Guinea, we had four clinical trial centres start efficacy evaluation at the same time.

Dr Marie-Paule Kieny (far left) alongside fellow researchers following an Ebola vaccine trial in Guinea

So in other words, phase two trials were effectively replaced by multiple phase one trials because of the need to save time.

Do you aim to implement that strategy for future epidemics as well?
Potentially, although of course we would need to formalise it beforehand, and also make sure we pinpoint which diseases could cause an epidemic. Ideally, the phase one and phase two trials will have been done in advance anyway, so you would have these results ready for when the outbreak struck – it's all about the preparation.

If a researcher is reading this and wants to get involved, how should they go about doing this? Will there be any fund-raising activities to gather more support?
We are doing a lot of advocacy work but we cannot just rely on investments from a single country – this is a global responsibility to ensure better preparation. We had a

consultation surrounding this in Oslo last year, and following that discussion some funders have come together to create CEPI – the Coalition for Epidemic Preparedness Innovations.

This is an initiative designed to create and test vaccines for epidemic diseases in advance of outbreaks. CEPI adopt the priority list of the Blueprint and they are now seeking funding.

So who will be the funders?
So far the Norwegian government is a funder, The Wellcome Trust, The Bill and Melinda Gates Foundation. A number of other governments could also join to make up this money, to help further research and development into vaccines.

Vaccines aren't the only area we are looking at developing though. Other investments into diagnostics will also be needed because, while having a vaccine is fantastic, you also need to have other things available to support it.

We will look to continually finance research because our R&D Blueprint is not an R&D product initiative – instead, it is a tool to convene, to discuss, to agree on norms, and to then develop these norms into an effective solution.

Looking towards the future, what kind of impact do you think we will see from your R&D Blueprint plan in say, ten years' time?
In an ideal world, the plan would be that, for all the diseases identified, there would be diagnostics ready to use, a number of laboratories in different places around the world able to diagnose said diseases, and vaccines at a point where their efficacy could be tested.

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What are platform technologies?

When an emergency strikes, it is important to have prior knowledge in place to come up with an effective solution. Imagine you were stuck up a tree – it would be better to know how to climb than not.

Platform technologies replicate this concept within epidemic outbreaks. By providing a platform of background knowledge against a particular disease, these technologies can be used to develop vaccines and techniques that can diagnose viruses, in almost a 'plug and play' format.

As Dr Kieny puts it: "If you need to develop something in an emergency, it's always better that there is some prior knowledge about the type of technology you use. So for example, if you want to develop a diagnostic technique against a new disease, platform technologies effectively mean you can just plug and play – you have a basic machine, a basic knowledge of how to develop diagnostic products, and then you just adapt accordingly.

"One of the technologies used by Johnson & Johnson against Ebola is based on an attenuated virus that has been used as an experimental vaccine for a whole number of other diseases, including malaria, HIV and tuberculosis. In effect, having these platform technologies in place potentially enables us to serve more than one disease.

"So in the middle of an outbreak if you say, 'I have this technology and now I will put in an Ebola gene', you can rapidly progress because you already have a lot of background knowledge about safety, efficacy and dosage, and you can start running tests immediately after an outbreak. One of the fundamental ideas for our R&D Blueprint plan is to identify platform technologies that could be used to rapidly generate effective products against unknown diseases, to combat the effect of epidemics."

Developing these platform technologies is a vital component of WHO's R&D Blueprint action plan. Working together with CEPI – the Coalition for Epidemic Preparedness Innovations – Dr Kieny hopes to ensure that techniques are prepared in advance of the next epidemic, especially in terms of determining technologies versatile enough to serve more than one disease.

Having these technologies in place ensures safety, efficacy and – perhaps most importantly of all – saves time. Dr Kieny says: "If you look at the vaccines which were developed for Ebola, there are numerous examples of how effective these platform technologies can be. There was, for example, the vaccine developed by GlaxoSmithKline which, similarly to the Johnson & Johnson vaccine, used an attenuated virus platform that had previously been used against malaria. We had far fewer questions to ask about this, because the technology had already been used before."

In other words, if you have a knowledge of the platform beforehand, it is much quicker and safer to develop vaccines, so that the reaction of the international community can be sped up when an epidemic next strikes.