LSHTM Viral
S3 E5: Who give the green light for COVID-19 vaccines anyway?
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SPEAKERS
Karl Byrne, Naomi Stewart, Annelies Wilder-Smith, Amy Thomas

Naomi Stewart 00:02
Welcome to LSHTM viral season three, podcast exploring the science behind global and public health. I'm Naomi Stewart.

Karl Byrne 00:11
I'm Karl Byrne.

Amy Thomas 00:12
And I'm Amy Thomas.

Naomi Stewart 00:14
And every fortnight we'll explore the latest developments in the covid 19 pandemic and take a deep dive into vaccines and vaccinations. Over 141 million people globally have tested positive for covid 19. Since the pandemic began, well over 3 million have tragically died. While the UK has undergone the first step of lockdown restrictions easing as of Monday, more than 10 million people in the UK - 19% of the total population - have now received their second dose of a COVID vaccine, while nearly 33 million have had their first dose. The UK government continues to commit that all adults in the UK should receive a first dose by July. The Joint Committee on Vaccination and Immunisation has issued new advice that pregnant women should be offered the Pfizer, BioNTech and Moderna vaccines at the same time as others in their age and clinical risk groups, keeping in mind that the MHRA issued advice two weeks ago that people under the age of 30 with no underlying health risks should be offered an alternative to AstraZeneca based on possible blood clot risks. Elsewhere, the United States has given the most single doses to its population - 209 million, followed closely by China with 192 million. India has given out over 123 million vaccine doses, but in the midst of a second wave have stopped

exporting AstraZeneca and the US continues to uphold their ban on export of raw materials needed to produce COVID-19 vaccines amidst growing criticism. A new variant B.1.617 was first found in India on March 24, and cases have now been detected in the UK. This variant will be closely monitored to determine if it is a variant of concern, as it involves two separate mutations. In today's episode, we speak to Professor Annelies Wilder-Smith from her home in Switzerland, about the approval process and regulatory mechanisms for approving vaccines amongst the world's largest ever vaccine related history. Welcome Anneliese.

Annelies Wilder-Smith 02:25
Thank you.

Naomi Stewart 02:25
So you're a Professor of emerging infectious disease here at the London School of Hygiene & Tropical Medicine. And you also sit on the World Health Organization's Sage Working Group on COVID-19 vaccines. Can you tell us first a bit about that group and what it does?

Annelies Wilder-Smith 02:40
So indeed, I work as focal point for the Sage working group and COVID-19 vaccines. It's a working group that serves Sage. So that brings together all the evidence and we have subgroups working on COVID-19 vaccines that look at vaccine impact modelling at the evidence gathering for all the vaccine trials and at privatisation. So maybe a little bit more background to Sage before I explain about our processes. So Sage is the strategic advisory group of experts to WHO that advises the WHO Director General on vaccine recommendations. They usually meet twice a year to go through all currently available vaccines for which there needs to be new recommendations or updated recommendations. So whilst regulatory authorities look at the question, if a vaccine should be used, a policy organisation like Sage looks at how should a vaccine be used. So Sage takes the totality of information into account then to recommend how best to use a vaccine. And remember that sometimes also includes making recommendations outside the available data are just based on modelling or based on common sense or based on expert consensus. So that is Stage.

Naomi Stewart 04:06
And so this process in the work that Sage does, is that after vaccines have been regulated, or is that prior to that?

Annelies Wilder-Smith 04:13
That's a very good question. That's exactly it's so it has to it has to come after. So a vaccine has to be approved by regulatory authorities. Or if it's a vaccine for an emergency of you know, like a public health emergency of international concern like COVID-19 now like Ebola in the past, who is also in a position to issue an emergency use listing after their own careful review. And with that condition in place, it's then that Sage makes recommendations. Obviously during this time of the pandemic, we work in parallel, so not sequential. We don't wait for the processes to have finished. We all start looking at the dossier in parallel, but we really wait for an official regulatory approval. So you will see that all the recommendations that we did for Sage for the COVID-19 vaccines were always in timely association with the FDA or with the European Medicines Agency.

Naomi Stewart 05:11
So thinking of those regulatory bodies, so mostly what's in the news is the national level ones. But can you walk us through what sort of bodies then exist in the world to approve these vaccines - who gets the final say on whether or not a country or a population or region like Europe has access to them?

Annelies Wilder-Smith 05:31
So every country has a regulatory body, but most countries will rely on what we call stringent regulatory authorities and WHO publishes a list of stringent regulatory authorities now for vaccines. Currently, the only stringent regulatory authorities are indeed FDA and EMA. And the European Medicines Agency - EMA - and WHO emergency use listing process benchmarks itself against the European Medicines Agency, there's an agreement that has been going on, you know, long before the current pandemic and the European Medicines Agency in return offers some services like for example, ensuring quality assurance of the GMP, you know, the good manufacturing processes, etc.

Naomi Stewart 06:14
So a lot of people around the world looking at this at the same time. And so when these regulatory agencies are deciding whether or not to approve a vaccine, what considerations are they looking at? What are they thinking about in saying yes or no?

Annelies Wilder-Smith 06:27
So for regulatory authorities, the main stage is looking at the efficacy and safety of the trials, which are derived from phase three trials, but then we'll also look at all the other phases. So starting from preclinical, I mean, just the platform, how was the vaccine developed to animal studies to immunogenicity studies. Now, the phase one, phase two are usually immunogenicity and small size safety studies, but then, really, it needs to translate into the efficacy trial and efficacies. Our estimates are derived from large scale with large populations involved for the phase three trials. So they will look at all this in totality, but they also look at what they call the CMC dossier. They look at a lot a lot consistencies. They look at the manufacturing processes, sterility, you know, is every batch of the same quality? All these issues the regulatory authorities look into. Once they're approved in every country. There are then groups that are now called national immunisation technical advisory groups - NITAGs - and there's also RITAGs - RITAG is a regional immunisation Technical Advisory Group. And then the global one is indeed Sage. Right. That's that's what the WHO Sage is. And so obviously, we all work together a Sage as representing WHO obviously focuses on global recommendations, and that sometimes, but not always, sometimes may differ from national or country specific considerations because epidemiology may be different, or some other other issues Overall, we all work in parallel, but also together, and there's a lot of communication between sage, the RITAGs and the NITAGs. The technical advisory groups, they really look how best to use the vaccine. So the questions they asked would be, you know, once we now know is approved, it's efficacious, safe, we know the vaccine characteristics and then we would deliberate upon what is the age group? Which populations should be prioritised? What's the dosing interval? What are the vaccine logistics? What are the contraindications to the vaccine? What are the precautions to the vaccine? What about subpopulations? Subpopulations include pregnancy - so pregnant women usually, you know, need separate considerations because of different issues. But it's also subpopulations like persons with underlying medical conditions, persons

living with HIV, persons with immune compromised states. Then the age groups, are there enough data for the extreme ages? So it means the very old or the very young. So this is what the policymakers look at. And then they issue a recommendation and that is then translated into the implementation.

Naomi Stewart 09:01
Just out of curiosity, who are the type of people that would sit on these regulatory bodies? What kind of backgrounds and expertise is they have?

Annelies Wilder-Smith 09:09
So regulatory bodies obviously need to understand all the preclinical issues, but also the clinical questions. So you need a range of expertise. For the policymakers, you will always need clinicians, epidemiologists, vaccinologists, disease specific specialists. So for COVID you will need to understand COVID, or measles or polio and often ethicists,

Naomi Stewart 09:34
So quite a diversity then in the types of perspectives.

Annelies Wilder-Smith 09:39
It's very interdisciplinary is a range and also just like to know for Sage, it reflects this interdisciplinary nature.

Naomi Stewart 09:47
And so on COVID-19 there have been sort of public concerns have been aired about the vaccine and why people might be hesitant to take it or have any issues around taking it. And a lot of that has to do with the short time span. So can you walk us through how from this perspective, of approving, how it happened in such a short time span compared to other vaccines we've had. And if people do have a reason to be concerned?

Annelies Wilder-Smith 10:13
For most vaccines in the past, we went sequentially. So you've done phase one, and you move to phase two and phase three, then the regulator's, then the policymakers, then the implementers. So what we have tried to do for this emergency, and what we also did for the Ebola, is we're trying to go in parallel, so we collapse certain steps. But what we have not done, and that's important to communicate, nobody has taken any shortcuts for the phase one, phase two, and phase three trials. And they are the pace limiting factors. But what the regulator's did, so we started we call it rolling review. So instead of waiting for the final result, the manufacturers would give us the dossiers as a rolling review. So every time there was more there were more data accrued, you know, more data were then submitted so that you don't start from scratch. We all started working in parallel and looking at the data in parallel. But what indeed is happening, all these vaccines are not approved fully licenced - they all have undergone emergency use authorization. So emergency use authorization means you look at the totality of data available at the time, but you recognise that some of the questions still need to be addressed, and then need to be addressed post authorization. So basically, there's a condition for conditional marketing approval contingent upon the manufacturers being obliged to submit a risk management plan, but also contingency plan and also a plan of research questions that still need to be

addressed. And that they will still need to address. So obviously, for the COVID-19 vaccines, while we have shown efficacy in all the age groups that we wanted to show and also have shown safety in the phase three trials, what we don't have is duration. So the minimum duration that regulatories has specified is a median of two months of observation time. So with that, obviously, we do not know what the duration is, you know, we don't two months at the time of approving, which means we need to continue following up the vaccinees, but also need to instate other studies to look at the effectiveness over time. Because the question that we still need to address is, you know, is there a need for and what is the best timing of booster doses. In terms of safety, we know from basically all vaccines that the safety concern is within the first 28 days post vaccination. And for this, we have sufficient data. In fact, most of the vaccine adverse events are usually within the first week. But obviously, we also need to follow up for rare or unanticipated or unknown adverse events that could come up later on. That's much more difficult to ascertain, though.

Naomi Stewart 12:55
And so a lot of governments they've been sort of flip flopping when it comes to AstraZeneca in particular and taken away the approval they've previously given it and then re-implemented it. So why would a government do that? And what sort of impacts does that have on the confidence a population might feel in a vaccine if it comes in and then it goes out?

Annelies Wilder-Smith 13:16
Yes, so this is a very difficult situation. And it's about weighing up trade offs, and different countries will decide differently, and there's no black and white answer. So when you have a safety signal, that is still very, very low number compared to the you know, the millions of doses given. There are two ways of deciding one way is - Oh, well, we'll just pause until we know and understand better. So we have to do an assessment. We call it a causality assessment, and look, look at all this data and it takes time, then some counties will decide, well, let's hold the whole programme until we have more data. And then we can restart it when we have more data. Other countries or regulatory authorities will say - it' small number, we all expect a certain number of adverse events in the population that is older. Remember, we are vaccinating an at risk population. Where we know by definition, there is a very high background rate of health problems, regardless of vaccination. And it could just all be very coincidental. Some countries may then decide - well, but we'll still continue with the programme and just follow up any problem. I think there's no right and wrong here. But there are consequences and the consequences when you hold a programme that you undermine public confidence. So the communication around holding opposing a vaccination programme to assess adverse events always is difficult and could be misconstrued by the media, by the public that is concerned. But on the other hand, we also have to say if you do not pause, because there was a safety signal and it emerges that indeed it was a real issue, then it also undermines public confidence in vaccines. I do think that showing the surveillance does work. We picked up rare events out of millions of doses given - it means our surveillance is extremely good and should actually enhance confidence. The public should know well, the regulators are taking any safety signal seriously and are working on it. I personally think the media should really communicate this in a positive way. And then if we find out that the safety signal was not a safety signal or the safety signal was an acceptable level within the public health vaccination programme, then we can reinstall such vaccines. But I totally agree with you, the flip flop has not helped the programme and there is now again an increasing vaccine hesitancy for such vaccines.

Naomi Stewart 15:38
Yeah, and I've definitely been hearing sort of bit of unnerved perspectives from family and friends on AstraZeneca. But thinking about the other vaccine. So the big thing with COVID is the approval of the mRNA vaccines which have not been approved for public use before in your role. And just thinking about it in general, were there special considerations around approving a vaccine if it's an mRNA versus the other types of vaccines?

Annelies Wilder-Smith 16:03
So you're right in the sense that mRNA is a relatively new platform. So regulatory authorities were unfamiliar with this platform. At that said, though, the oldest studies and the trials and the phase three trial of both mRNA vaccine - Pfizer and Moderna were really conducted at at very high standards. And the dossier submitted to the regulators but also to us at WHO Sage were impeccable. These were good dossiers, in fact, it made our lives easy. They had very good data on the age groups that we are interested in, on the immunogenicity, on the safety and the efficacy results, as you know, were just compellingly good. So we were relatively expedient, therefore, in approving and issuing policy recommendations for those vaccines. You need to keep in mind though, that for the mRNA vaccines, we have seen an unusual high rate of anaphylaxis, which means it's a severe allergic reaction. And therefore these vaccines need to be given under observation. So all the Pfizer and the Modena vaccines need to be observed for 15 minutes, because we know the allergic reactions usually happen within 15 minutes. But even just you know, observing every vaccinee for 15 minutes is a logistical nightmare, you know, you really want to have a rapid throughput, right. But here, you're obliged to observe these vaccinees for 15 minutes. And all vaccines, all COVID-19 vaccines are quite reactogenic, I think we need to be transparent about it, we need to communicate it. So reacoigenic means really, a vast majority of vaccinees have quite severe arm pain in local injection, site pain, swelling, redness, may feel fatigued, may have a fever, and may be off work for a day or two. But it all resolves. I think that's important. You have to be honest and transparent and say - Look, expect the side effects, we know that they exist, don't be surprised. The most important communications obviously, that overall the vaccines are very safe and efficacious. And seriously, the risk of all of us of getting COVID-19, as a disease is so extremely high. And also the risk even for younger people to have long COVID or have some some kind of consequences post-COVID is very high. And then for those of us are at higher risk, because of higher age, or underlying medical conditions, the risk benefit of this vaccine is so much in favour of the vaccine that we don't even need to discuss further, it is so much in favour of this vaccine. And so that is for us as individuals, but and also as a population, as countries, as governments - we want to go out, we want to be back and lead normal lives. We want to be out of this lockdown, whatever measures we have, and there's no way around it, then getting high vaccine coverage rates. The vaccine is the answer for us to get out of this pandemic. And that needs to be communicated in a way so that people embrace the vaccine in a positive way.

Naomi Stewart 18:55
Yeah, certainly. And I'm very much looking forward to when I get the opportunity to have one as well. Have you had the vaccine yet? Have you had the opportunity?

Annelies Wilder-Smith 19:03

Oh, I wish I would. So I'm so in Switzerland. I am still not eligible. In fact, because of the extreme supply constraints in a wealthy country, like Switzerland, where at this current moment, only 75 years and above are eligible, or patient fronting health care workers. And I'm not patient fronting - I work from home for WHO Sage so I'm you know, I'm not at high risk of exposure. I'm personally not eligible, but I can tell you I registered and I send them an email every week - "When is my turn?"

Naomi Stewart 19:38
That's fantastic. They have a thing in the UK where some of the vaccine centres, if people don't show up for their appointments, they have a couple leftover at the end of the day. So I've been standing in the queue waiting just in case but no success yet.

Annelies Wilder-Smith 19:50
That is fantastic. And in fact that should be done. You don't want to have wastage of one of the most precious public health tools at the moment, and I think the more the more flexible we become in our programmes, the better.

Naomi Stewart 20:01
Absolutely. So just thinking overall, what would you say is key for the public to understand about the approval process when it comes to COVID-19?

Annelies Wilder-Smith 20:13
I think that the public needs to understand that that we did not cut corners. That we've gone through the full processes, where we have gone faster was in working more in parallel with rolling dossiers with several bodies working in parallel with lots of coordination and communication between agencies between expert groups, etc. I think the world is working extremely hard. You know, we all work overnight or weekends. I heard yesterday from friends at the MHRA in the UK in December, really worked around the clock to make sure that that they had reviewed all the data and issued timely recommendations. But we also need to know that we need to continue looking at these vaccines, even after introduction and that we still need to learn a lot. But we also need to make sure that the world and the sense we need to embrace even, you know more platforms, more vaccines, newer vaccines, because any single vaccine platform cannot deliver on the vaccine supply that we need. This is the historic biggest vaccine roll out that the world has ever seen. Remember that we usually just vaccinate children's cohorts, certain age groups here. We want basically to vaccinate the whole world, especially the adult world and the older people as fast as possible so that we can stop and prevent those deaths, but also protect the healthcare system by being overwhelmed because of this high number of the tsunami of hospitalizations. So speed is needed whilst we need to continue with our scientific rigour and our also vigorous approval processes.

Naomi Stewart 21:48
Great, thank you, Annalise. That was very helpful and informative.

Annelies Wilder-Smith 21:51
Thank you, Naomi. Thank you.

Naomi Stewart 21:54
And thank you listeners for tuning in to another episode of LSHTM Viral. If you like what you're hearing, please do subscribe. And if you're listening on Apple podcasts, leave us a rating and review. We do welcome audience questions at comms@lshtm.ac.uk. However, if you do have questions about specific medical conditions or your own health, please speak to your GP or doctor for medical advice. Stay tuned for our next episode in two weeks on how vaccines are manufactured, including at the scale needed to vaccinate the entire world against COVID-19. Until then, stay safe and informed,