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Building Global Pediatric Research Networks

This podcast episode features a discussion on the article "Building Global Collaborative Research Networks in Pediatric Critical Care: A Roadmap," published in Lancet Child and Adolescent Health in February 2025. The conversation, led by Dr. Jeff Burns with guests Professor Luregn Schlapbach and Professor Padmanabhan Ramnarayan, explores the challenges and strategies for creating effective global research networks in pediatric critical care. The speakers highlight the importance of collaboration, the need for a robust evidence base, and the potential of large data models to drive the future of precision medicine and improve patient outcomes.

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Sarah Marcley *00:04*
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Jeff Burns *00:18*
Welcome to the OPENPediatrics Podcast. I'm Jeff Burns from Boston Children's Hospital and the World Federation of Pediatric Intensive and Critical Care Societies. Today, we're going to be discussing an article that appeared in Lancet Child and Adolescent Health in February of 2025 entitled "Building Global Collaborative Research Networks in Pediatric Critical Care: A Roadmap". And we're very pleased to have with us today, the two senior authors of that manuscript, Professor Luregn Schlapbach is affiliated with the Children's Hospital of Zurich and the University of Zurich in Switzerland. Luregn, welcome to OPENPediatrics podcast.

Luregn Schlapbach *00:58*
Thank you so much, Jeff. It is a pleasure to be here.

Jeff Burns *01:02*
And also with us today is Professor Padmanabhan Ramnarayan from the Imperial College London and the St Mary's pediatric intensive care unit. Ram, welcome to OPENPediatrics podcast.

Ram Ramnarayan *01:15*
Hi, Jeff. Thanks so much for inviting me. It's great to be here.

Jeff Burns *01:20*
Your publication gained a lot of attention from colleagues across the world because it, quite frankly, didn't fit the mold. It's not a classic clinical investigation. And instead, you were documenting in a

descriptive way the rather deep and vast research network, networks that exist across our field and across all of the continents. And I have to say, in my memory, in the current era, I think this is the first time I've seen such a comprehensive description of the vast research networks. But as if we take a step back, you know, could I ask him, maybe, beginning with you, Luregn, what was your motivation to do this? Why did you undertake this?

Luregn Schlapbach *02:06*
Yeah, so this, this work originated in some ways, actually witnessing how much the adult ICU research landscape had been affected and changed by the COVID 19 pandemic. So, you know, we've witnessed within the first one to two years of the pandemic, a very rapid growth of very high quality ICU trials, enrolling large numbers of patients across many countries, sophisticated designs such as, you know, platform trials. And this has really changed the paradigm actually how ICU trials in adults are being conducted. And when we discussed this in in you know, amongst colleagues and researchers or at conferences, we realized that there's a real risk that pediatric ICU as a community is actually not catching up with that pace. That said, at the same time in the last decade, there's been a number of really large trials in particular, employing pragmatic designs in our field, which have been published by a number of research groups, in particular, the UK clinical trials group or the INDeX pediatric study group, for example. And so it's becoming more obvious that as as an ICU community for children, we can do trials, but we have not really done trials together, and we don't really have a strategy to do trials together in an effective way that can meet the needs of of the patients that we care for around the world, and this need is probably going to get even more accentuated, as in the last decade, more and more services, in particular in Latin America and as well Asia, have started, actually to offer critical care support for critically ill children, which before were not there. So we have actually a very expensive, you know, specialty, looking for of the very high risk patients that is expanding in numbers and at the same time, actually, the evidence base for what we currently do is still actually too slim. So the question was, really, you know, how can we change that? Ram, do you have anything to add to that?

Ram Ramnarayan *04:21*
Yeah, I think we felt that this was an opportune moment to bring the individual countries or regional networks into a common umbrella, not necessarily to duplicate some of the work that they're already doing. And I think we know that there are several networks across the world who are doing clinical trials, but also observational studies. They're all at various stages of maturity. What we wanted to do was to bring them together under a common umbrella so that we could identify what is commonly applicable across the world that we could address together. And I think the key point here is about collaboration and the success that we could achieve through collaboration, rather than duplication or competition or, or trying to do much of the same things less effectively.

Jeff Burns *05:11*
Well, as we speak, I currently hold several hats, but one hat that I hold is that I'm the President of the World Federation of Pediatric Intensive and Critical Care Societies. And as you know, we're a society of societies around the world, and I have access to colleagues throughout the world because of WFPICCS. But one of the things that's been very difficult for us, WFPICCS, to nail down is exactly where are all the active research networks. And so that's why I'm so intrigued by what you undertook. And so if you could tell us, how did you do this, how did you identify who the active research networks were, and, and what were the barriers to trying to understand whether they should be pulled forward as

part of what you detailed in this manuscript in The Lancet in February of 2025, or not. Ram, could you take that?

Ram Ramnarayan *06:10*
Yeah, I think that we were fortunate, because a lot of work had already gone into working together collaboratively as part of the surviving sepsis work and sepsis guidelines and sepsis definition work. So we had some awareness of all the regional and national networks, but we also used a cascading approach to ask people who they knew were leading networks. And what we wanted to do was to give the opportunity for every part of the world to be represented. So we wanted to make sure that we didn't under represent specific areas. We wanted to invite two representatives from each of these networks that we identified, so that there would be a clear steer from from the network, and also clarity that these representatives essentially were representing their network, and they would take back everything that was discussed, back to their networks for endorsement, for ratification and discussion. And so in that way, we put together a group of 32 members within this collaborative group, they represented 20 countries, all the continents, and they were all actively published research networks, so they had already published some work as a group. We found some challenges in Africa, for example, where there wasn't a particular research network, but we had some active publishing groups from South Africa, from other parts of Africa. So we we flexibly adopted a model where we didn't specifically say, well, you have to have a network there, but we asked for representation from some of these published groups, with the hope that this would spur them on to think about developing a network in the future.

Luregn Schlapbach *08:05*
What's maybe worthwhile is that, I mean, there are networks like PALISI, for example, or INDeX PSG, or the UK PICS Study Group, which have become really well known because of their ability to do trials, but in the last years, in particular, as well, you know, in South America, for example, through BRnet-PIC then, or, you know, the LARed network. Or as well, in Asia, through PACCMAN, there's been actually very important large networks built who have become very effective in doing observational studies. And these colleagues approached us and said that, you know, we're really keen now to move as well towards interventional trials, but you know, we need to exchange to gain access to expertise and to not to reinvent the wheel. And so I see a real power here that we we really have researchers working in the field of pediatric critical care together, from, from the entire world, with, you know, with a heavy focus on, on trialists, or on sites you know, which are keen to do trials. However you serve. Actually, it's a bit of a mix of a bottom up and a top down approach, in the sense that the initiative was really started, you know, bottom up. But then we went to the networks to make sure we have their endorsement. They could recommend people. However, we were keen, actually, to have a good mix in terms of experience, discipline, then region.

Jeff Burns *09:40*
Well, you identified the active networks, but then, of course, the real hard question begins, and that is, what's the landscape of what's being done and what should be done? And in your manuscript, you came up with a series of concepts, but what was the process that you utilized amongst these 20 something research networks to identify what is being done and where the gaps are, especially knowing that you're dealing with research networks that span low and middle income and high income countries where the priorities are different.

Luregn Schlapbach *10:17*

So we formed subgroups within, within the working group, and one was tasked to assess the changing pediatric critical care landscape. Second one to look at the evidence base, the third one to identify challenges, and the fourth one to think about solutions, which then led to work and leading to the action plan, but maybe to focus a bit on the first three groups first, then the PICU landscape has really been changing, changing in the last one or two decades. So on one side, as already mentioned, there's been a rapid increase in number of PICU services, in particular, as well in in countries outside in North America, Western Europe and, and Australia. And these face particular challenges in terms of, you know, geographical conditions, training conditions, access to resources, but they're actually caring for very large populations. At the same time, there's been a trend, in particular in high income settings, that the proportion of technology dependent or highly complex, highly comorbid patients has proportionally increased then, and that's the, the impact of rare diseases and congenital conditions in the PICU is often now outnumbering, actually, you know, common acquired conditions, such as, you know, trauma or infections. And this actually has been coupled, you know, with changing as well ethical situations, issues of staff burnout and questions as well, you know, on the financial liability of expensive healthcare systems, right? All of all of which justify a strong need for a better evidence base. However, if we look at the quality of that evidence base, it's not really that great. So the working group assessed some of the recent guidelines that had been issued, actually, for our field, such as, you know, pediatric ventilation liberation bundles, the bronchitis guidelines, PANDEM guidelines, fluid surviving Sepsis campaign, nutrition, traumatic brain injury and and ventilation PALICC guidelines. And if you look at all these recommendations, there's a very, small number of strong recommendations which are actually based on evidence. And so there's a real mismatch between the needs of our fields, the risks to patients as well, you know, the cost of the disciplines that the long term implications and the evidence base for what we have. And so the question is, you know, how, how can we change this? And maybe, maybe, Ram, I mean, your group in the UK has been tremendously successful in the last years running trials. And can you, can you tell us a bit about some of the problems you've encountered and, and because these, in many ways, I think are typical for our field.

Ram Ramnarayan *13:25*
Yeah, I think some of the challenges that we faced in the UK are very similar, as you say, to what other countries are facing. Our cohort is heterogeneous. We have patients of different ages, different sizes, different diseases, and in general, the size of our cohort is much smaller than adult ICU, for example, maybe by a fold of 10 or 15. So any studies that we do have to be collaborative in nature. There is no real practical way in which we can actually achieve a successful trial with a few centers, it would have to be a large collaborative effort. Resources and funding is obviously a big challenge that I think probably resonates with everybody's experience. We have a fantastic system in the UK of the National Institute of Health Research, which has, over the last 20 years, become our primary funder for healthcare research, and also has a research delivery network. So every hospital, for example, has research nurses who are centrally funded, who you don't have to apply separately for grant funding for because there's already somebody in your hospital employed as part of a core group of people who would then deliver your trial for you or your study for you. So that results in efficiencies that not obviously all systems and all healthcare systems and all other countries might be able to replicate. I think the other challenges we've faced, which are again, very common, I'm sure to everyone else, are issues around consent for emergency recruitment of patients, most of what we do in pediatric critical care is time sensitive, and interventions can't be deferred and left for Informed Consent discussions, and in fact, there is an increasing justification for using research without prior consent in a lot of emergency trials, and we have used some of those models, as have other, other countries and other

research networks, but that's variable, and I think that because of regulatory and other differences between countries that can be different across the research networks, and we found that, as part of our discussions, that in some countries that was acceptable, some countries it was not possible. I think ethical challenges, particularly around what interventions can be offered to critically ill children at what stages. Industry collaboration, which is very limited in our field, we don't really have much industry collaboration. We are not testing novel drugs and novel therapeutics and novel diagnostics all the time. That's a big challenge. So those came out as some of the common central themes when the group got together and looked across the world.

Luregn Schlapbach *16:30*
And what Ram has just explained us, you know, has created a situation where we're probably not learning as much as we could as a discipline. So compare this to a child coming into hospital and that gets diagnosed with leukemia. You would be completely unimaginable to enroll this patient in just an off label treatment without being on a trial. And that's the reason that oncology has achieved tremendous, not just survival advantages, but, you know, a highly efficient research infrastructure, and the impact that goes way, way beyond just the, you know, the acute care. So the question is, how could we as as a discipline for caring for critical children, make sure we can learn much, much quicker, and that that we reduce the number of children exposed to potentially harmful or treatments, or that we reduce the costs due to potentially unnecessary treatment, and that we increase the children which benefit actually from targeted treatments, which which make a difference for them. And with that in mind, it's, it's essential that we we identify, actually, strategies to to tackle this. There are some challenges which, in fact, around the world are relatively similar. You know, treatments such as oxygen or fluids, antibiotics, even you know, types of of respiratory support are actually pretty much used around the globe in services that can provide some degree of acute care support to children. The evidence base for many of these treatments or thresholds when escalation should happen, for example, or therapeutic endpoints, often this evidence base is very, very limited, right? And so there are some some low hanging fruits or common questions that that would be great to to address together. And if we could create this evidence in a more generalizable way that we are sure actually findings are relevant, not just for you know, the units where it's where they've been created, but actually that findings can be applied to broader patient groups that potentially could save thousands, thousands of lives and potentially be cost saving and and really accelerate the learning of our discipline.

Jeff Burns *18:56*
Well, I have to say that what you both have just described in the last 10 minutes, I think, is one of the most succinct and frankly accurate descriptions of where the field of pediatric critical care medicine is in 2025 across the world and and that's not a criticism of our world, that we're not as evidence based as our pediatric oncology colleagues are, it's rather a description of why are we not and so now I turn to you really outlined a roadmap in your, your manuscript, the way forward. Ram, could you explain that? What is the way forward from here?

Ram Ramnarayan *19:42*
It's really great question. Jeff. I think it was very fortunate to have all these people sit together, put their heads together and come up with a really tangible action plan for our specialty. So we came up with seven actions. I'll go through them individually. Not in a lot of detail, maybe, but the first one was, clearly we needed to create an entity, which was a global network of research networks. We needed to have this entity created that put together all the research networks. They came together in a

collaborated way. And we gave ourselves a time frame of doing that, by the end of 2024, and I think we, it's fair to say that we have now formed that network. There's a little bit more work to be done in terms of, you know, developing it further. The second action we put in place was we would have a web based library where we could share across international boundaries what work is ongoing in each of the networks, what is already done, what is ongoing and what is being planned. So for example, we would be able to quickly look at this resource and tell ourselves that there are three trials on fluid management, for example, going on across the world. There are two more sepsis trials being planned in the next two years. I don't think currently we have a real time visibility of this, other than through hearsay and through talking to people and word of mouth. The third action is to establish what we called an observatory. So this is a global pediatric critical care research observatory, where we put together resources around common research priorities. What would be common to all the countries and all the networks that are part of this, this group that could be amenable to global collaboration? How could we plan on a global trial, for example, clearly with something maybe as specific as, let's say, dengue fever, it's not going to be applicable to the whole of the network, but something such as respiratory support, as Luregn alluded to earlier, might be something that applies to everyone. Everyone ventilates children, and maybe that's a common starting point for us to look at. A common theme. We said in action point four that we would develop some harmonized minimum data sets and core outcome sets that everybody can use for clinical trials if they did, and those together. So this means we would come up with a common data dictionary, common set of data to collect for the trials that we could then share very quickly across the world. And the fifth point was something much more aspirational, which by the end of 2028 we said we would want to build a platform trial infrastructure across two regions or two regional networks. And what this effectively means is that at least in two regions, we could run platform trials that could be merged and become multi-platform collaborations. Ambitious, but I think there's already work starting to happen on this front and so we are optimistic that this is an achievable action point, and then action point six is more about funder advocacy. I think across the world, we know that funding for pediatric critical care research is a challenge. It's tough. We have to convince national funders. But if we are talking globally, we have to convince global funders. And who would we go to? Would we go to Bill and Melinda Gates Foundation? Would we go to the World Health Organization? Would we go to individual countries funders and patch together a net— a patchwork of funding that worked across the globe? I don't think we have an answer, but I think without advocacy, we are not able to progress this. There are some good examples of transnational funding schemes. So for example, the UK NIHR has announced a scheme where it funds trials across UK and Australia, or UK and Switzerland, and so countries would have to pair up to apply for these grants. And so it transcends the national boundaries, but what we really wanted was a global system that we could apply for. And then finally, the seventh action plan, which I think is probably a very important action plan, is collaborating to understand how we can implement the findings of all the research we do into our practice, because we know that there is a massive gap between even the amount of evidence we have in our specialty and how actively we implement it in our daily practice. And I think that is a big challenge, because there is no point doing research if we can't change our practice and improve patient outcomes, and we thought that that was a very important but challenging, complex action plan to look at.

Jeff Burns *24:50*

Well, that's a very ambitious pathway forward, but clearly outlining the steps necessary to make a successful global network. Can you add some more specifics. Luregn, can you add some more specifics, maybe to this list on how this this could happen, what needs to happen.

Luregn Schlapbach *25:07*
Currently, when you look at reasons why larger trials are often not done, people say, well, it's too hard because we sent you. We need to reinvent the wheel and build up all elements from from, from zero, right? And what this network essentially should achieve in the first place is that it exchanges resources that it allows to build capacity and that that we use, we start using similar tools to do trials. Education may be an aspect on how to do trials. Then some some modular aspects on data dictionaries, for example, is another element, or as well, you know, things such as, you know the REDCap setup. So alone, this will actually make it much easier, in particular, for colleagues that do not have access to a well-run trial networks such as Ram has them to to even just participate in trials, or do trials right? Through this we we should be able to really as well, to make mentorship happening. That that colleagues, for example, from South America, can really benefit from mentorship and and be supported in in running their trials, and be supported as well that trials which are done actually are well designed, robustly designed throughout, right, and ideally, that we move away from every region doing its own trials to then actually saying, Look, guys, we're really interested to look at, you know, steroids in this or that situation, for example, then let's discuss who else is actually keen on doing this? And by this that we really gain efficiency. Then what Ram mentioned in terms of the platform trial infrastructure? Of course, this is much more ambitious then, but this is actually then the ultimate infrastructure step to have essentially perpetual infrastructure, which is not bound to just one study question, right? And so in many ways, it's collaborative. What it actually should achieve is that we move away from one group, one interest, doing one trial, and the whole effort goes into this, and that's been it to rather saying this collaboration should lead to an ongoing facilitation of trials, which makes actually every trial easier. And so that we move from a current state where you know the child coming in with shock, where you start fluids, inotropes, ventilation, steroids, whatever, it's based on local preference and some evidence-based guidelines, right, that this moves within five years to say, you know what these are the steps we actually have evidence for, and that, thereby, you know, we can deliver better care. In order actually to achieve this, there's one aspect which, which we haven't spoken so far. But I think what can be very powerful in the prioritization of tasks and then in convincing as well clinicians on on the importance and selecting the right interventions and the outcomes is really as well how we work with patients and families. And we've realized, for example, simply by these first exchange is that there are vast differences in in experiences with patient and public involvement, but as well in the regulatory requirements for such and that's a very, very simple but probably quite fundamental example of how exchange across networks can really, you know, help speed up, right? And when it ultimately then comes to saying, okay, we we don't just want to do trials to publish. We want to do trials which change how we do critical care, which change outcomes for patients. So we need to future proof already the trials by incorporating implementation at the outset. You know, Oxy-PICU is a good example. We now have the first large trial, which gives us evidence on, on, you know, benefits of certain saturation targets, right? But having spoken to colleagues, you know, many, many units around the world have not necessarily implemented these findings. So, you know, why? Why is that? If we want to learn as a discipline and improve to save to, you know, save lives of children, that means as well, we need to become better at really taking evidence generated serious and making sure we can implement it. And that's one task to it within our institution. But then actually, if we want to face this at the global level, you know, we we have to learn in different ways. Now, all of what we've said so far is very important,

already in the current state, but it will be even more pressing in the next decade, when actually many will try and move more towards precision medicine. You know, for us as a pediatric critical care discipline, to have any chance to really be engaged and make a difference for precision medicine for children, we really need to be ready, right? We need to be ready to apply large data models, to apply novel biomarkers, use highly precise treatments if we want to make sure we can do this actually specific for kids. And so in some ways, it's a real call to action that we start making this now happen.

Jeff Burns *30:31*
You've just outlined really such a forward looking but absolutely necessary path that our field must take. Ram, any final comments on you know where we are and where we need to go?

Ram Ramnarayan *30:48*
The process of getting together everyone across the world into a network, just the process of getting everybody together, discussing the challenges we face, realizing that everyone's challenges are common and we face similar challenges, we have similar outlook on how we can learn from each other, I think has itself been very illuminating and really instructive. I think that the process of collaboration is really people getting together and sharing their experiences, and that itself has helped many of us, every one of us probably, to advance our own vision of what we wanted to do across the network. So I think that this is a very useful journey, a very enlightening journey, and hopefully a very productive journey for us as a group, that wherever we get to with this group, I think we will have learned and achieved a lot.

Jeff Burns *31:52*
We've been discussing a manuscript that appeared in Lancet Child and Adolescent Health February edition of 2025 entitled "Building Global Collaborative Research Networks in Pediatric Critical Care: A Roadmap", with the two senior authors, Professor Luregn Schlapbach from the Zurich Children's Hospital and Zurich University in Switzerland, and Professor Padmanabhan Ramnarayan at the St Mary's Children's Hospital and Imperial College London. Ram, Luregn, really, this has been a terrific overview of not just describing research networks, but clearly indicating that you both have the foresight to see where our field is and needs to go now in order to really advance care for children across the world. And so on behalf of all of our listeners on OPENPediatrics, I thank you for this work, and the foresight, again, that you both had to undertake it and the effort that you're leading. And I will also add that WFPICCS is redesigning its website as we speak. We have a new vendor, a new platform, and that one of the things that we want to do is to provide a kind of a living registry of your networks listed here, so that people have at least one place to go to know, how can they find out who's doing what around the world? So we're determined to do our part to help advance your goals with this effort. So thank you very much for being with us today on the OPENPediatrics podcast.

Luregn Schlapbach *33:24*
Thank you so much, Jeff. It's been a real pleasure, and I would like to just thank everyone that has been part of this collaborative group for international trial collaboration.

Ram Ramnarayan *33:36*
Yes, and likewise, Jeff, thank you so much for inviting me, and it's been absolutely fascinating to have an instructive discussion about the global collaboration that we can achieve.

Sarah Marcley *33:47*

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ARTICLES REFERENCED

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