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Unresolved Controversies in Child Pneumonia in low and middle income Countries.

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Abstract

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There has been a fall globally in pneumonia-related fatality in children during the Millennium Development and early Sustainable Development Goal era.

However, pneumonia remains the single largest contributor to mortality with issues including antibiotic resistance, pollution, a change in infective epidemiology, equipoise over effects of adjunctive treatments and identification of sick, decompensating children.

This thesis examines 4 of these controversies as original research.

Theme 1; two papers, 1 and 2: The first discusses the background motivation. The second a large randomized, non-inferiority controlled trial undertaken ('RETAPP') in a suburban slum area of Karachi, Pakistan. Oral amoxicillin treatment was compared with placebo, in the treatment of WHO-defined, uncomplicated, fast breathing pneumonia.

Theme 2 (paper 3) The role of indoor air pollution and poverty in recurrent fast breathing pneumonia: a nested case control study.

Theme 3 (paper 4). The role of adjunctive use of zinc to standard treatment in children with severe pneumonia: a systematic review and meta-analysis of randomised controlled trials.

Theme 4 (paper 5). Recognition of the child with severe respiratory illness using the Clinical Respiratory Score in the emergency department

Results: In the RETAPP study, 4,002 randomised children were enrolled. There was a significant difference in treatment failure rates in the amoxicillin and placebo groups (2.6 % vs 4.9 %). The number needed to treat was high at 44, and mortality very low and similar in both groups, discussion points for policy makers.

There does not appear to be an enhanced risk with Indoor Air Pollution in recurrence of pneumonia. The only predictor was household poverty: external pollution could be a factor.

Adjunctive zinc confers no additional advantage to children with severe pneumonia.

The clinical respiratory score is a highly sensitive, but non-specific marker for severe illness.

Conclusions: The small, though significant, differences in treatment failure rates in fast breathing pneumonia are likely to have implications for setting of management.

The role of environmental predictors needs to turn to poverty and external pollution.

Zinc has no role as an adjunctive treatment. The clinical respiratory score has excellent predictive value for severe illness.

Keywords: Paediatrics, pneumonia, global health, antibiotics, poverty, risk scoring

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Jehan F, Nasir I, , Kerai S, Brown N, Ambler G, Zaidi AKM. Should fast breathing pneumonia cases be treated with antibioics? The scientific rationale for revisiting management in Low and Middle Income countries. Int J Infect Dis. 2019 Aug;85:64- 66. doi: 10.1016/j.ijid.2019.05.035.

II Jehan F, Nisar I, Kerai S, Balouch B, Brown N, Rahman N, Rizvi A, Shafiq Y, Zaidi AKM (2020) . Randomized Trial of Amocillin for Pneumonia in Pakistan. New England Journal of Medicine 383:24-34. DOI: 10.1056/NEJMoa1911998

III Brown N, Rizvi A, Kerai S, et al. Recurrence of WHO-defined fast breathing pneumonia among infants,its occurrence and pridictors in Pakistan: a nested case–control analysis. BMJ Open 2020;10:e035277. doi:10.1136/

IV Nick Brown, Antti Kukka, Andreas Mårtensson. Efficacy of zinc as adjunctive treatment for pneumonia in children in Low and Middle Income Countries: a systematic review and meta-analysis. BMJ Paediatrics Open 2020;4:e000662. doi:10.1136

V Kanwal Nayani, Rubaba Naeem, Owais Munir, Naureen Naseer, Asher Feroze, Nick Brown, Asad I. Mian. The clinical respiratory score predicts paediatric critical care disposition in children with respiratory distress presenting to the emergency department. BMC Pediatrics (2018) 18:339. https://doi.org/10.1186/s12887-018-1317-2

Contents

Abbreviations

WHO	World Health Organisation
LUS	Lung ultrasound
PCR	Polymerase chain reaction
IMCI	Integrated Management of Childhood Illness
IAP	Indoor Air Pollution
GAPPD	Global Action Plan for Pneumonia and Diarrhoeal Disease

Introduction

Despite major advances in Global Public Health and improvements in individual case detection and management, pneumonia remains the single numerically largest cause of mortality in children in Low and Middle Income Countries.

Much guidance has, traditionally, been empirical and pragmatic, has on occasion lacked an evidence base and, as a result, become controversial

This thesis provides the background to the current situation (advances and setbacks) globally and examines four issues in five manuscripts which have been conspicuous for the debate around each: the need for antibiotic treatment in fast breathing pneumonia; the role of indoor air pollution in recurrent pneumonia; the role of adjunctive zinc treatment and the validation of a readily administrated respiratory risk assessment tool, not previously formally tested in a Low and Middle Income Country.

Chapter 1

History

Letter to the British Medical Journal December 1902

The Natural History and Treatment of Pneumonia 'Sir,

This very common disease has been brought before us in the British Medical Journal lately, and no one can doubt that it is still deserving of, and requires, study. From careful observation of the temperature I recognized that some cases ran their course in four days, when the exudation cleared up as if by magic; others had a longer course, in which the exudation became purulent, and did not end before the seventh or tenth day, or even longer. I regarded these cases as identical in cause, and thought they varied in duration owing to the state of the exudation-looking upon those which got well in four days as analogous to a wound which heals by first intention and those which took longer to wounds which did not heal by first intention.

From recent researches, however, it would appear that some pneumococci give rise to a semi gelatinous exudation, while others produce an exudation consisting of cells. The former pneumococci were derived from lobar pneumonia and the latter from lobular pneumonia. If such be the case, then it is evident that it may be possible by watching the course of each case to tell which kind of pneumococcus has been the cause of the disease. The pneumonia that follows influenza in no respect resembles ordinary pneumonia, and there can be little doubt that its pneumococcus is a most dangerous one, and probably allied to that which causes the pneumonia following measles - a most fatal form. Such facts as bacteriology show how necessary it is that the natural history of every disease should be most carefully studied by every practitioner. As to the treatment of pneumonia, there is little new, as we learn from Sir Dyce Duckworth's lecture; but, since it is now regarded as a specific fever, its treatment ought to be conducted on the same lines as scarlet fever, etc.; and as there is no more efficacious remedy in specific fever than cold affusion. it ought to be used in the acute stage. Sir Dyce Duckworth recommends sponging with iced water in preference to the cold bath in cases of hyperpyrexia, but having learned (as it were by accident) that it is the shock

or stimulus given to the nervous system which does good when cold water is applied, and not the lowering of the temperature, whenever it is thought safe to do so, a pail of cold water should be suddenly thrown over the patient in a tub or bath. I have seen it act like magic in scarlet fever of the worst type on the second day of the disease; and wherever the application of cold seems advisable, there can be no doubt that cold affusion, as introduced by Dr. Currie, is the best way in which it can be applied - I am, etc', Hawick, Dec. 1st. John Haddon, M.D. (Haddon, 1902).

Pneumonia through the ages: early history to the 1990s

Pneumonia is derived from the Greek pneum (lung), and literally means, therefore 'a disease of the lungs', though is now used largely in the context of inflammation caused by infection.

Records of pneumonia date as far back as Hippocratean Greek history in the 4th century BC (Perkins 1964). The illness has been intertwined with human history since. William Osler, the father of modern medicine, described it in 1901 as 'the new captain of the men of death', ousting the previous captain (coined by Bunyan) of 'consumption' or tuberculosis. He made this assertion on the basis of estimates in the US of an estimated 76,490 deaths (187 per 100,000) a figure greater than that attributable to TB (Reynolds 1903). Ironically, Osler was himself to succumb to pneumonia some years later, his terminal illness also chronicled in the British Medical Journal.

'It was on December 12, 1919, that Osler, who was suffering from a prolonged and obscure disease in his chest, sent for him to come to Oxford. It was a shock to see him very ill and emaciated, in a state of extreme toxaemia, and speaking little because speech brought on a bout of paroxysmal coughing. Osler himself had jotted down for his information, in that terse fashion of his, some pencilled comments on his own condition. Seven days previously the chest had been punctured and a little serous fluid drawn off without any relief of symptoms. Lord Horder postulated the presence of an interlobar empyema, and the puncture was repeated, using the longest needle procurable at the time. The same sort of fluid was forthcoming and that only in small amount. The condition remained relatively unchanged for another week, so that he made up his mind that something further should be done by way of exploration. A couple of extra long needles were made, Osler readily agreeing to the exploratory "seance". The first puncture was negative, but the second was successful, and when the stylet was withdrawn Osler himself said, "You've got it, my boy". Between 4 and 5ml. of stinking pus was withdrawn. On the following day Charles Gordon-Watson drained an abscess cavity. The drainage, never very copious, ceased three days later. No further collection of pus was revealed by a second operation. Four days later the end came in dramatic fashion. He (Lord Horder) had talked with Osler in the morning, and

had then gone to lunch downstairs, when the nurse called him quickly, and ongoing upstairs he found that the dressings and the bed were soaked in blood. The sepsis had opened up the wall of a small vessel in the upper lobe of the lung, and Osler died a few hours later that day' (Ancaster I.1920).

Had he lived thirty years later, Osler might well have survived this illness. Unfortunately for him, treatment of pneumonia in this era was (as this account describes) essentially symptomatic and supportive. Though antisera (first discovered in the 1880s) were available for diphtheria and tetanus, Streptococcus Pneumoniae was more evasive and it was not until the 1920s that specific antisera became available. Even at this stage though, it was a high risk and expensive procedure and far too labour intensive to be deployed extensively. During the era of the Second World War, during which antibiotics first became available, events moved fast and the prognosis of pneumonia infection changed (Podolsky 2005). By 1939, the first sulphonamides in the US were available, the excitement leading the New York public health advisory committee to declare "It would seem that the captaincy of the men of death is being passed on rather rapidly these days. I don't think pneumonia will rank as more than a sergeant in another year or so." (Russell 1940) The succeeding twenty years saw the sulphonamides being superceded by the penicillins followed by a generation of (what could be fairly called) naivete and complacency. Levels of pneumococcal resistance to penicillins in the US were of the order of 3.6% in 1987, but by the early 1990s had increased exponentially to 24% of invasive disease isolates (Podolsky 2005).

In parallel with (but somewhere behind) the advances in antibacterial treatment, the history of vaccination was evolving: though pneumococcal polysaccharide vaccinations were developed as far back as the 1940s, it was not until the appearance of protein-polysaccharide conjugates in the 1980s and 1990s that population seroprotection was afforded. They now form part of the routine immunisation schedule of almost every country worldwide, Haemophilis Influenzae B vaccination being universally adopted since 2000 and, by 2017, pneumococcal conjugate vaccine (PCV) used in the programmes of 141 countries (Wahl, O'Brien 2018).

I will discuss the evolution in antibiotic and vaccination issues in more detail in the epidemiology chapter.

Chapter 2

Pneumonia in children: global epidemiology

Context

The Millennium Development Goal (MDG) era saw a number of advances in the pre specified target areas. Of the original 8 goals, at least 5 were directly relevant to child health. These included: MDG 4 - the reduction of child mortality by two thirds from the 1990 level of 90/1,000 live births; MDG 1 – the abolition of poverty and hunger; MDG 2 - universal primary education; MDG 3 - gender equity; and MDG 6, combating malaria and HIV (UNICEF, WHO 2000). All the initiatives were retained in some form in the Sustainable Development Goal (SDG) plans for the 2015-2030 era.

About 80 percent of the world's under-five deaths in 2011 occurred in 25 countries. Of these approximately half occurred in 5 countries: India, Nigeria, Democratic Republic of the Congo, Pakistan and China (McAllister, Liu L et al 2018, Lassi 2014). Preventative strategies generic to illness phenotypes include: exclusive breastfeeding; safe complementary feeding; universal vaccination, water, sanitation and hygiene (WASH), preventative zinc supplementation in children and vitamin A supplementation in deficient populations. Modelling estimates that scaling up of existing interventions against the two disesases to 80% and immunization to 90% would eliminate more than two-thirds of deaths by 2025 at a cost of US $6•715 billion by (Bhutta, Chopra and Mason 2013).

Troeger and the 2017 Global Burden of Disease Infections Collaborators estimated that the factors responsible for the greatest decrease in under-5 pneumonia mortality between 1990 and 2017 were: increased coverage of vaccination against Haemophilus influenza type b (11•4%); increased pneumococcal vaccine coverage (6•3%) and reductions in household air pollution (8•4%) (GBD 2017 Lower Respiratory Infections Collaborators 2020).

Child pneumonia contributes approximately 30% of the total global pneumonia mortality (Boloursaz and Lotvian et al 2015) but, despite a gradual recent fall in both incidence and case fatality rates over the Millennium Development Goal (MDG) era (1990-2015), acute lower respiratory tract infection (ALRI or ARI) or pneumonia remains, by some distance, the single largest contributor to global post neonatal mortality (UNICEF 2018, García-

Elorriaga and Del Rey-Pineda 2015, Leung and Chisti 2016, Bryce 2005). It is a disease of poverty, strongly related to household overcrowding (da Fonseca Lima, Gonsalves Mello 2016) with undernutrition increasing case fatality (Tuti, Agweyu 2017).

This situation, however, has improved since the start of the Millennium Development Goal era in 2000 and continues to do so. In 2013, the incidence of community–acquired childhood pneumonia in Low and Middle Income Countries (LMICs) was an estimated 0.22 (IQR 0.11-0.51) episodes per child per year of which 11.5% progressed to severe episodes ((Nair, Simoues 2013). Rudan and O'Brien 2013). In 2016, there were an estimated 120 million illness episodes per year and between 880,000 and 935,000 deaths, the vast majority in LMICs where resources are inherently more stretched and populations more vulnerable. (UNICEF 2018, Zhang, Sammon et al 2016). Of other major causes of child mortality, only acute gastroenteritis to which an estimated 9% of deaths are attributable is comparable (Leung and Chisti 2016). Recent pooled data from 89 studies including 14•9 million episodes of severe and very severe pneumonia cases (data from 2010 before classification was modified) estimated 265,000 (95% CI 160,000-450,000) in-hospital deaths. The vast majority of these deaths happened in LMICs and, although 62% of children with severe ALRI are treated in hospitals, 81% of deaths happened outside hospitals (Nair, Simoues et al 2013).

Recent estimates are more encouraging. The number of episodes of clinical pneumonia in young children decreased by 22% from 178 million (95% uncertainty interval [UI] 110–289) in 2000 to 138 million (86–226) in 2015 and, Over the same period, the burden of clinical pneumonia attributable to HIV decreased by 45%. Identification, intervention and observation became more active with a rise in global hospital admissions for childhood pneumonia increasing by 2•9 times, the increase particularly marked in South-East Asia. Most importantly, deaths have fallen from 1•7 million (95% UI 1•7–2•0) in 2000 to 0•9 million (0•8–1•1) in 2015, the majority in India, Nigeria, Pakistan, Democratic Republic of the Congo, and Ethiopia (McCallister, Li et al 2019). More recent data collected by the Global Burden of Disease Group in 2017 estimated 808,920 deaths (95% uncertainty interval 747,286–873,591) in children under 5 years old. In parallel, there was a fall in the risk factor exposures: non-exclusive breastfeeding, crowding, malnutrition, indoor air pollution, in- complete immunisation, and paediatric HIV (Reiner RC et al 2020, King, McCollum 2020).

This figure might be an underestimate as case ascertainment relies on either presentation to a health facility or a well conducted verbal autopsy (Brown 2015): if neither occurs, a pneumonia death might be attributed to other causes though the reverse could happen too. Lack of follow up may be another cause of underestimation of burden of disease as mortality may not occur until some time after the acute episode. In the Gambia, Chhibber found that severe

malnutrition and anaemia independently predicted post discharge mortality (Chhibber, Hill et al 2015).

Though appropriate management of childhood pneumonia can reduce pneumonia–specific mortality (Chopra, Mason 2013) the disease places a large economic burden both at societal and family levels particularly resonant in resource–constrained LMIC health settings (Zhang, Sammon et al 2013, Rudan, O'Brien et al 2013, Liu, Oza et al 2015, Bhutta, Das et al 2013).

A changing landscape: capsular polysaccharide vaccinations

The epidemiological landscape has undergone rapid change and much recent information has been provided by the multicenter, clinical and laboratory focused Pneumonia Etiology Research for Child Health (PERCH) study (Driscoll, Karron et al 2017).

The epidemiological landscape has undergone rapid change. With the widespread introduction of the Haemophilus influenzae type b and multivalent pneumococcal conjugate vaccines (PCVs), a greater proportion of cases of pneumonia are now viral (Williams 2018, Bolosourz and Lotfian 2015). In South Africa, von Mollendorf and colleagues saw major changes in invasive disease associated with the introduction of PCV 7 and, later PCV 13, an era in which HIV interventions were also being improved. They estimated a change in cases of severe pneumococcal pneumonia (defined by need for admission) from 107,600 cases per year (95% confidence interval [CI] 83,000–140,000) in the pre-vaccine (2005-2008) era to 41,800 (95% CI 28,000–50,000) in the immediate post PCV introduction years and a fall in pneumococcal annual deaths of 61 per 100,000 child-years (von Mollendorf, Tempia et al 2017).

A recent estimate by the 2017 Global Burden of Disease Infections Collaborators suggests that 2 of the 3 factors responsible for the greatest decrease in under-5 pneumonia mortality between 1990 and 2017 were: Haemophilus influenza type b vaccination (11•4%) and increased pneumococcal vaccine coverage (6•3%) (GBD 2017 Lower Respiratory Infections Collaborators 2020).

Despite vaccination, however, most deaths, are still caused by the main bacterial agents, S. pneumoniae (33 %) and H. influenzae type b (16%) (Bolosourz, Lotvian et al 2015, Rudan, O'Brien et al 2013). A recent study by the WHO CHERG group estimated that in 2015 there were 294,000 pneumococcal deaths (uncertainty range [UR] 192,000–366,000) and 29 500 Hib deaths (18 400–40 700) in HIV-uninfected children aged 1–59 months world- wide. Pneumococcal deaths declined by 51% (7–74) and Hib deaths by 90% (78–96) from 2000 to 2015, most children who dying of pneumococcus (81%) and Hib (76%) having presented with pneumonia.

Approximately 50% of all pneumococcal deaths occurred in four countries in Africa and Asia: India (68,700 deaths, UR 44,600–86,100), Nigeria (49,000 deaths, 32,400–59,000), the Democratic Republic of the Congo (14,500 deaths, 9,300–18,700), and Pakistan (14,400 deaths, 9,700–17,000). They concluded that the widespread use of Hib vaccine and recent introduction of PCV in countries with high child mortality has reduced Hib and pneumococcal cases and deaths, but that progress towards further reducing the global burden of Hib and pneumococcal disease burden would depend on the efforts of a few large countries in Africa and Asia (Wahl, O'Brien et al 2018). Programmatic introduction of a vaccine, of course, does not necessarily equate with coverage at the individual level. A recent example includes the recent systematic review, by Tricaciro in which marked differences in uptake of PCV in Lower Middle Income Countries and Upper Middle-Income Countries (UMICs) (71% and 48% respectively) were found. These were felt to be largely due to an unsuccessful "transition" of MICs from GAVI assistance to GAVI independence. This arises as countries cross the income eligibility threshold and is compounded by a lack of country- specific data on disease burden, a lack of local economic evaluation expertise and the cost of the vaccines were identified as the leading causes of the slow uptake of PCVs in MICs. (Tricaciro, McNeil et al 2017).

Respiratory syncytial virus (RSV) is now the most common pathogen. Murdoch et al estimated that RSV is present in about 29% of all episodes of ARI followed by influenza (17%) and other respiratory viruses including adenovirus, metapneumovirus, coronavirus and adenoviruses (Murdoch 2016). A recent Lancet review by Shi et al that in 2015, RSV accounted for 33•1 million (uncertainty range [UR] 21•6–50•3 million) episodes of RSV-ALRI, 3•2 million hospital admissions, and 59600 (48,000–74,500) in-hospital deaths in children younger than 5 years (Shi, McAllister et al 2017).

Most (and, to date, this includes SARS- Cov- 2) viral pneumonia is self-limiting, requires only supportive treatment and is not helped by antibiotic treatment. Avian (epidemic) influenza (H1N1) for which oseltamivir is beneficial if administered early is an exception.

These changes in aetiology as well as rising antibiotic resistance have clear implications for management, issues to which I will return in the thesis specific controversies section.

A changing landscape: antibiotic resistance

Another major change in global infectious disease epidemiology has been the increase in antibiotic microbial resistance (AMR). Resistance (a natural evolutionary response by viruses, bacteria, fungi and parasites) occurs through four main mechanisms: limiting uptake of a drug, modification of a drug target, inactivation of a drug, and active efflux of a drug. Though beyond the

scope of the thesis, specific examples include: beta lactams, macrolides (efflux), macrolides, aminoglycosides (phosphorylation) and quinolones (acetylation) (Zaman, Hussein et al, 2017).

Much recent information on the global situation is based on the WHO 'GLASS* (global antibiotic resistance, use surveillance system) surveillance program to which 82 countries contribute (WHO 2020). Pakistan is one of the collaborating countries, has high reporting cover from the participating laboratories with the exception of s.pneumoniae and, on the basis of resistance analysis has been deemed high risk for multidrug resistant tuberculosis (MDR TB). These data, however, span all age groups and lack granularity partly, no doubt, due to the lack of a national antibiotic stewardship programme. More information is available from the data and summaries in the Global Antibiotic Resistance Programme (WHO-GARP 2020). Though incomplete, there are clear policy implications. The increased perception of third generation cephalosporins and fluoroquinolones, as a "cure-all," by both physicians and the public leads to over prescribing and spill over to the use of second line agents, carbapenems, tigecycline, linezolid and vancomycin usually reserved for last resort situations. The situation is compounded by barriers to creating an AMR program (Center for Disease Dynamic, Economics and Policy 2018).

Recent work in the post-neonatal age group shows a high prevalence of non-susceptibility to treatment advocated by the WHO therapeutic guidelines in gram positive infections. Should this continue to increase, standard beta lactam (and even new generation cephalosporin) therapy will become redundant (WHO 2015, Williams, Isaacs et al 2018, Downie, Armiento et al 2013, Isaacs and Andressen 2013). Gram negative infections are even more problematic given the relative paucity of treatment options. Though data is scarce (GLASS 2020, CDDEP/GARP 2018) there is evidence that some drugs are already redundant.

Sepsis can be a complication of and is often clinically indistinguishable from pneumonia. A recent systematic review and meta-analysis of antibiotic resistance patterns in community acquired sepsis resonates with other findings (Downie, Armiento et al 2013). Susceptibility was determined to the antibiotic combinations recommended by WHO: benzylpenicillin/ ampicillin and gentamicin; chloramphenicol and benzylpenicillin and third-generation cephalosporins. A total of 19 studies from 13 countries, with over 4,000 blood culture isolates were identified. Among neonates, Staphylococcus aureus, Klebsiella spp. and Escherichi coli accounted for 55% of culture positive sepsis. In infants outside the neonatal period, the most prevalent pathogens were S aureus, E coli, Klebsiella spp., Streptococcus pneumoniae and Salmonella spp., which accounted for 59% of culture positive sepsis. For neonates, penicillin/gentamicin had comparable in vitro coverage to third-generation cephalosporins (57% vs 56%). In older infants (1–12 months), in vitro susceptibility to penicillin/gentamicin, chloramphenicol/penicillin and third-generation cephalosporins was 63%, 47% and 64%, respectively. They

concluded that the rate of community-acquired resistant sepsis is a major global public health concern.

Though it is already late, antibiotic stewardship is one key area. In essence, stewardship involves: appropriate antimicrobial use; using the narrowest spectrum agents for the shortest courses reasonable to prevent resistance. Strategies to promote stewardship in the management of childhood pneumonia were summarised by Ngueyn, Hoang et al (Nguyen, Hoang et al 2017) and include: enhanced regulation; education; surveillance and the removal of financial incentives for disbursement.

Changing landscape: Coronavirus pandemic: potential implications

Work on this thesis began in 2018, well over a year before the SARS-Cov-2 variant corona virus was first recognized and reported in Wuhan Province, China in December 2019. Once it had been though, it was only a matter of weeks before the illness (Covid 19) had been afforded pandemic status by the WHO. Since then, the infection has been the overriding global public heath priority (Alwan, Burgess et al 2020, World Health Organisation Covid statistics 2020).

At the time of completing writing (early January 2021), there have been 79 million cases and 1.7 million deaths worldwide (WHO Covid statistics - weekly update from 20.12.29). Case fatality rates appear quite consistent, but the new variant mutation appears more transmissible.

So far, severe cases have been, numerically, overwhelmingly adult. The reasons for children being relatively protected are still unclear, but might include differences in natural immunity, previous corona exposure, a lower proinflammatory tendency and lower airway epithelium angiotensin converting enzyme receptor density. The severe illness trajectory in adults includes an Acute Inflammatory Respiratory Distress Syndrome, usually a pneumonic illness often with multiple organ failure. High risk groups are the elderly, obese and hypertensive (Klein JD, Koletzko B et al 2020).

Though children have much milder disease, a recently recognized new acute inflammatory illness has demonstrated that complacency would be inappropriate. It has some similarities with similar to Kawasaki's disease but in general has more systemic manifestations and generally affects older (teenage rather than pre-school) children. It is (rather confusingly) called either multi-inflammatory-systemic illness associated with Corona (MISC) or (UK terminology) Paediatric Inflammatory Multisystem disease temporally associated with SARS-Cov 2 (PIMS-TS). MISC (first reported in April 2020) has been temporally associated with SARS-Cov-2 in many children on the basis of IgG or IgM seropositivity (Goetzinger F, Santiago-García B et 2020).

The numbers are, so far, small and causality yet to be established, but the picture may, of course evolve in parallel to the ongoing randomized treatment trials These include the 'Recovery' study in which children with severe disease are being randomized in specific limbs such as dexamethasone and (the anti-interluekin 6 monoclonal antibody) tocilizumab (recoverytrial 2020).

We are, though, still learning as an international case series published just a couple of weeks ago on a previously unrecognized inflammatory demyelinising illness temporally associated with Covid testifies (Lindan, Mankad et al 2020). More unanticipated, temporally associated illnesses seem certain to follow.

Controversies in children include their role (as asymptomatic carriers) in spreading the virus, and their own household risk from a positive adult contact. Both appear very small as does the risk in asymptomatic children 'spreading' the virus at school, but most governments have enforced at least temporary school closures, measures with huge negative implications for education, nutrition and wellbeing (Munro A, Faust S 2020).

The relative risks in LMICs are, still, unclear. To date numbers are lower than in HICs: this might be real or a reflection of under diagnosis or under-reporting or, even death before presentation.

What is certain is that children in LMICs will continue to experience problems as a result of secondary or collateral damage, examples including: disruption to routine health programmes (vaccination); primary and secondary care; disruption to schooling (implications for education, nutrition and early child marriage) to lockdown associated issues (mental health and child abuse) and a reluctance by parents to attend health facilities they would otherwise have used out of fear of infection resulting in late or non-presentation for non-Covid illness (Bhutta, Hauerslev et al 2020).

At the time of writing, multiple treatment trials have been completed. None have shown consistent superiority over standard treatment, but dexamethasone in severe disease and remdesivir in moderate disease in adults have been approved (Beigel, Tomashek et al 2020, Rubin, Can-Tack et al 2020).

The last month has seen the dissemination of the results of a number of high profile vaccine trials and the approval of several Covid vaccinations. Mass vaccination has already begun in the US, UK and EU countries but achieving full coverage including booster doses will take many months, if not longer, even in the most active programmes (Rubin and Longo 2020).

Chapter 3

Pneumonia: physiology

Though pneumonia can be caused by a wide range of infectious organisms and environmental agents, there are a number of common pathophysiological pathways, all of which are, essentially inflammatory. These involve the pleura, bronchi, alveoli and vasculature of the lungs (Scott, Brooks 2008). Immunosuppression from any cause including malnutrition, HIV, underlying malignancy or immune modulating treatment increases susceptibility both to infection and to mortality as a result of infection.

A number of processes ensue from this initial insult:

Hypoxia

Alveolar consolidation causing sub-optimal aeration and a ventilation-perfusion (VQ) mismatch leads to hypoxaemia, a low partial pressure of oxygen in the blood. This often (but not always) leads to hypoxia, the state of inadequate tissue oxygenation. The VQ mismatch can be exacerbated by a number of factors including: respiratory muscle fatigue, secretions, impaired cough, and, in young children, a poorer central respiratory response to hypoxia and hypercapnia (Duke, Mgone et al 2001, Onyango, Steinhoff et al 1993, Usen, Weber 1999). The cascade can become irreversible.

Hypoxia is difficult to judge clinically. Assessment depends largely on the presence of cyanosis, a sign dependent on the degree of desaturated haemoglobin. In the presence of anaemia (very common in LMIC settings), this only appears when hypoxaemia is severe.

Inflammatory response

A detrimental host immune response can result in sepsis, worsening intrapulmonary shunting, Acute Respiratory Distress Syndrome (ARDS) and myocardial suppression. Children are inherently more susceptible immunologically due to a combination of: lower responsivity to pathogen associated molecular patterns; diminished antigen presentation; less avid natural killer (NK) cells; lower complement levels; poorer T cell function; lower interferon and cytotoxic CD* T cell response and lower specific

polysaccharide antigen response, all features that mature until adolescence. (Randolph and McCulloh 2014).

Chapter 4

Pneumonia-case definition and algorithmic management: background and context

Though, the terms are often, rather confusingly, used interchangeably, pneumonia and acute respiratory infection (ARI) are not the same entity. ARI is a broad definition including any anatomical part of the airway, larynx, trachea, bronchi, bronchioles and lung parenchyma. Most (but not all as several references and much literature testify) global data refers to ARI rather than pneumonia, which, strictly, is a lung parenchymal (alveolar) disease with or with- out airway involvement.

The signs of pneumonia particularly in young children are non-specific: sepsis, anaemia, malaria and congenital and acquired heart disease can all result in illness phenotypes that are very similar (Scott, Wonodi 2016) and can, of course, co-exist.

Algorithm based WHO guidance dates back to the 1980s. From the outset, it has (deliberately) been aimed at case recognition in LMIC settings by health workers with limited training. The syndromal definitions later became incorporated in the Integrated Management of Childhood Illness (IMCI) recommendations which first appeared in the mid 1990s (WHO 2010). Though the magnitude of effect of IMCI is still debated because of the inconsistency in coverage, there is concordance as to its contribution to improving mortality as case presentation level (Rakha, Abdelmomein et al 2013, Chopra and Mason 2013). The signs for pneumonia recognition were and remain an amalgam of relatively easy-to-measure signs in the primary health care setting: age adjusted respiratory rate thresholds and the presence or not of chest in-drawing are appropriate for oral antibiotic management. Oxygen saturation monitoring is still deemed ‘optional’ rather than ‘mandatory’. If there are additional danger signs compatible with ‘very severe’ pneumonia (poor feeding, lethargy, convulsions) admission and parenteral treatment is advised. These composite criteria, however, are imperfect, all to an extent being subjective. Even respiratory rate has degree of interobserver variability with 95% limits of agreement up between −7.1 and 7.0 breaths/minute (Daw, Kingshott et al 2017) and inter recording measurements highly environment dependent. Context (for example differences between noise, wakefulness, agitation and whether feeding) has been shown to explain 42% of the inter-child measurement variability (Muro,

Mutove 2017). Video recording (not currently widely available) can improve measurement error (Muro, Mosha 2017) but, almost invariably, involves a delay in intervention.

Pneumonia, acute lower respiratory tract infection (ARI) with lung parenchymal involvement is challenging from as diagnostic and, therefore, incidence comparison viewpoint. Diagnosis, strictly requires chest X ray but, most global epidemiological studies are based on the acute respiratory infection (ARI) clinical- syndromal diagnosis.

Radiological changes, though imperfect and subjective may augment these signs. Analysis of 4,232 children in the 'PERCH' (Pneumonia Etiology Research for Child Health) study showed that abnormal chest x rays were significantly more common in children with hypoxaemia (aOR 1.94, $p < 0.001$), tachypnoea, abnormal auscutatory findings and fever (Fancourt, Knoll et al 2017). However, for logistical reasons, radiology is often unavailable and as Lynch's systematic review showed, even in settings where radiology is available, a gold standard diagnostic test for bacterial pneumonia is a major unan swered area (Lynch, Bialy et al 2010).

Since 2010, two rounds of revisions to the IMCI guidelines have taken place, both based on expert consultation within the 'GRADE' (Grading of Assessment, Development, Evaluation) framework, changes that took place as the result of several factors. These included: the widespread availability of conjugate vaccines against Streptococcus pneumoniae and Haemophilus influenzae type b (Hib); a decline in maternal to child transmission of HIV and changes in criteria for the assessment of malnutrition, weight-for-height Z score (WHZ) and mid-upper-arm circumference (MUAC) replacing weight-for-age Z score (WAZ) (Agweyu, Lilford et al 2018).

In the first round of revisions which addressed management, new recommendations were made with regard to outpatient treatment of children in non- HIV endemic areas (WHO 2012). The main change was of the switch from co-trimoxazole (previously recommended for its Pneumocystis Pneumonia cover) to oral amoxicillin for fast breathing and/or chest indrawing pneumonia. The literature unequivocally suggested that this treatment was superior to co-trimoxazole and equipotent to injected ampicillin. In addition, oral treatment from a practical point of view, simplifies management as it can be home administered (Kabra, Lodha et al 2010, Grant, Campbell et al 2009, Haider, Saeed et al 2008, Haider et al 2002, Addo- Yobo, Chisaka et al 2004, Hazir et al 2002, Hazir T, Fox LM et al 2008, WHO 2014). The current recommendation is that dispersible tablets (more stable than liquid forms) of amoxicillin are used in a high dose of (rounded) doses of 40 mg/kg twice daily for 5 days. The guidance deliberately uses a low threshold for treatment in that the default diagnosis for a 'fast breathing' child is pneumonia requiring antibiotic treatment.

The next revision in 2014 addressed the previously subjective and often confusing severity categorization into three groups to two. Cases are now

divided into: fast breathing (formerly non-severe) with or without chest indrawing (the latter previously part of the severe group) pneumonia and severe a phenotype with danger signs (WHO 2014) The former can be safely treated at home with oral antibiotics (Hadi et al 2003, Ghmire, Pradhan et al 2010, Nsona, Mtimuni et al 2012, Bari, Sadruddin et al 2011). The latter requires parenteral (ideally observed and inpatient) treatment (WHO 2014). Fast breathing is defined by a timed respiratory rate over 50/minute in infants between 2 and 12 moths and >40/minute in children aged from 1 to 5 years. This guidance includes pulse oximetry measurement. Severe pneumonia requires fast breathing and/or chest indrawing and one of the following danger signs: oxygen saturation <90%, central cyanosis, severe respiratory distress, inability to drink or breastfeed or vomiting everything, altered consciousness, and convulsions.

Oxygen

Many children will be hypoxaemic and, most of those who are, also hypoxic. These children, however, might have no clear clinical signs. These children (and those who deteriorate from initial normoxia) require early aggressive oxygen therapy (through nasal cannulae, high flow humidified therapy, continuous positive airway pressure (CPAP) or ventilation) and are at high risk of irreversible progression without intervention.

Secondary care admission is recommended in part to monitor for and enhance earlier intervention in the case of deterioration and partly in order for reassessment by experienced physicians to rule out alternative pathology such as congenital heart disease (Agweyu, Lilford et al 2018).

Until recently, the result of patchy literature, heterogeneity and different saturation cut offs, though there was some evidence of enhancement of management. It was unclear whether monitoring improves outcome in terms of mortality (Enoch, English 2015). The benefits are now, however starting to become clearer. A recent deterministic estimate (Floyd, Wu et al, 2015) of the potential of saturation monitoring coupled with treatment if appropriate showed both good discriminatory value between severe and non-severe pneumonia, but also the potential to save up to 148,000 lives per year. More recently still, Colbourn and King et al in an analysis of linked community health worker, healthcentre and hospital admission and mortality data showed a strong predictive effect (independent of other WHO danger signs) on mortality of an initial with an adjusted Risk Ratio of 9.37 (95% CI: 2.17–40.4). Though the additional number of deaths at a cut off of SpO2 < 93% was small (so confidence intervals wide) it too was independently predictive RR, 6.68 (1.52–29.4). All deaths for which data were available occurred within 24 hours of arrival suggesting delay in seeking care is contributory. The limited amount of linked mortality data limits inferences (due to likely bias from the Null),

but the messages in terms of enhanced illness severity detection through the use of saturation monitoring unequivocal (Colbourn, King et al 2020).

Measurement of oxygen saturation improves prediction of severity, but is not yet widely available, though there is evidence from qualitative stakeholder data from Malawi, Sudan, Ethiopia, Cambodia and Uganda that fingertip devices and the acute respiratory infection timer are acceptable. Devices more dependent on a constant electricity supply were seen less favourably (King, Boyd et al 2018, Spence, Baker et al 2017).

There are a number of initiatives to improve distribution of saturation monitors including 'Lifebox', a low-cost, reusable robust, portable, battery operated oximeter which can be used with standard boxes (for example Massimo) or the Lifebox equivlant as well as smartphone interpreted devices. These are both acceptable and have a performance in terms of time to first plausible saturation reading comparable to more expensive counterparts, 70% and 63% of readings being made within a minute using the Lifebox probe and the Mssimo or Lifebox box respectively (Boyd, King 2018, King, Mvalo 2019).

Algorithmic performance

The overall performance of the IMCI algorithm in terms of mortality reduction in LMICs in Sub Saharan Africa and South Asia is not clearcut (Agweyu, Lilford et al 2018, Agweya, Agweyu, Opiya et al 2012, Mulholland, Carlin et al 2014). In a relatively high mortality setting, Agweyu et al assessed relative risks of death in 16,162 patients according to a number of a priori specified predictors for children with pneumonia according to severity grading. The mortality of those with non-severe pneumonia (321 of 11,788) was 3% and of those with severe pneumonia 14% (488/3,484). They found three predictors not currently included in the algorithm that were strongly associated with mortality: severe pallor (adjusted risk ratio 5•9, 95% CI 5•1–6•8), mild to moderate pallor (3•4, 3•0–3•8), and weight-for-age Z score (WAZ) less than −3 SD (3•8, 3•4–4•3).

Other factors independently associated with death were: WAZ between −2 and −3 SD, age less than 1 year, lower chest wall in-drawing, respiratory rate of 70 breaths per min or more, female sex, admission to hospital in a malaria endemic region, moderate dehydration, and an axillary temperature of 39°C or more (Agweyu, Lilford et al 2018). These findings make a strong case for future modification of the algorithm at least in high mortality, malaria endemic regions with a high burden of malnutrition. Severe pallor has a sensitivity and specificity of 80 % in predicting severe anaemia in children with low (< 15% packed cell volumes/PCV) (Weber, Kellingray et al 1997) which is itself a marker of chronic illness (undernutrition, helminth burden and malaria) and,

by extrapolation, is a proxy for vulnerability. Though the new guidelines are simpler, the downgrading of chest wall indrawing in particular has been controversial (Mulholland, Carlin et al 2014) and the guidance is likely to continue to evolve.

Chapter 5

Diagnosis

The diagnosis of pneumonia in field settings remains essentially a clinical diagnosis. There are, however, a number of additional measures that can refine treatment after initial management

Imaging

X Ray

Pneumonia, acute lower respiratory tract infection (ARI) with lung parenchymal involvement is challenging from a diagnostic and, therefore, incidence comparison viewpoint. The diagnosis is often purely clinical-syndromal and, though chest X ray considered equivalent to a gold standard, it is often not available in a field setting. X ray has been used more in validation studies and neither Infectious Disease Society of the US nor the WHO IMCI guidance recommends its routine use (Rees, Basnet et al 2020).

Radiological changes, though imperfect and subjective may augment these signs. Analysis of 4,232 children in the 'PERCH' (Pneumonia Etiology Research for Child Health) study showed that abnormal chest x rays were significantly more common in children with hypoxaemia (aOR 1.94, $p < 0.001$), tachypnoea, abnormal auscutatory findings and fever (Fancourt, Knoll et al 2017). However, for logistical reasons, radiology is often unavailable and as Lynch's systematic review showed, even in settings where radiology is available, a gold standard diagnostic test for bacterial pneumonia is a major unanswered area (Lynch, Bialy et al 2010).

A recent meta-analysis of individual predictors examined 10 hospital based validation studies including more than 15,000 children hospitalized in departments with signs suggestive of pneumonia. In these departments, X ray was routine and the agreed standard for consolidation compatible with pneumonia was of opacification in a whole or part of a lung lobe. Of the total, 24.9% (n=3743) had radiographic pneumonia. Age-based tachypnoea had a pooled sensitivity of 0.92 and a specificity of 0.22 for radiographic pneumonia lower chest indrawing a sensitivity of 0.74 and specificity of 0.15; oxygen saturation a sensitivity and specificity of <90% was 0.40 and 0.67,

respectively, and for a cut off of < 85% sensitivity of 0.17 and specificity of 0.88 Specificity improved when individual clinical factors (tachypnoea, fever and hypoxaemia were combined) but with loss of sensitivity. In short, though tachypnoea was moderately specific, no single sign or symptom was strongly associated with radiographical consolidation (Rees, Basnet et al 2020).

Ultrasound

There has been considerable excitement about the potential role of lung ultrasound (LUS) in the diagnosis of pneumonia in High Income Countries (Lissaman, Kanjanautom 2018,). There is, to date, little data to guide use in LMICs, but, recent work in Lima, Peru by Ellington on children presenting with pneumonia to a hospital outpatient and emergency department was encouraging. Using X ray as the gold standard, LUS had a sensitivity of 88.5%, specificity of 100%, and an area under-the-curve of 0.94 (95% CI 0.92–0.97) when compared to radiographically-confirmed clinical pneumonia.

There is likely to be more data available soon from collaborations (amongst others) in Bangladesh, Uganda, Mozambique and Pakistan (Lennahan, Volpicelli 2018) Given the relative ease of administration and interpretation compared to chest X ray, this technique clearly has potential, but, like any new practical technique needs to be validated in terms of user variability, gold standard comparisons and, ultimately randomized controlled trials.

Microbiology

Standard treatment is, by its nature, empirical. It is primarily beta lactam based to afford relatively narrow spectrum cover (less risk of resistance) for the most virulent bacterial pathogens. In the past, these have been S. pneumoniae and H. influenzae, but the advent of vaccination against common serotypes has changed the epidemiological landscape. Though less prevalent, antibiotic resistance has increased (Scott, Wonodi et al 2016).

Treatment should ideally be directed by a microbiological diagnosis, but, in reality, in children this is rarely obtained. An ideal sample is one of infected lung parenchymal tissue, uncontaminated airway secretions or blood culture. The former requires sputum (spontaneously produced or evoked by hypertonic saline) bronchoalveolar lavage which is rarely an option. Airway secretions are notoriously difficult to obtain without upper airway commensals (though the presence of polymorphs is suggestive of genuine infection) and blood culture hampered by lack of facility, culture media or, simply volume of sample (García-Elorriaga, Del Rey-Pineda 2016). In light of the Covid pandemic, it has become routine to additionally take nasopharyngeal and

throat swabs for polymerase chain reaction (PCR) analysis for SARS-Cov-2 in children presenting with respiratory symptoms (particularly if admission is required) in many HIC settings.

Polymerase chain reaction (PCR) also known generically as Nucleic Acid Testing (NAT) is the most promising group of new tests. It requires only small amounts of blood, is quick, is less affected by prior antibiotic administration and can show antibiotic sensitivity. It can be obtained from any normally sterile site including airway secretions, blood and urine (Chang, Ooi 2013, García-Elorriaga, Del Rey-Pineda 2016, Murdoch 2016). Their greatest use is in the detection of non-colonising bacteria such as Legionella and Mycobacterium Tuberculosis (MTB) and respiratory viruses (Murdoch 2016). The 'Respiratory MultiCode–PLx Assay (RMA; EraGen Biosciences)' for example combines multiplex PCR and microsphere flow cytometry to allow simultaneous identification of eight groups of respiratory virus: respiratory syncytial virus; parainfluenza; influenza A and B; rhinovirus; enteroviruses; metapneumovirus, corona and adenovirus B, C and E. It increases the probability of a positive finding by approximately three times (Scott, Brooks et al 2008, Lee, Gindle et al 2007).

Cytokines

Though, to date, only available in research settings, advances in cytokine assessment are worthy of mention. As part of the inflammatory response, a rise in interleukins and granulocyte colony stimulating factor (G-CSF) is common and the extent correlated to disease severity (Hauge, Chandyo et al 2015) These tests are still in their infancy, however, and cannot currently be used to guide individual treatment.

Combination kits appear more sensitive and specific than individual tests. Examples include: the ELISA-based ImmunoExpert™assay (MeMedDiagnostics, TiratCarmel, Israel) which measures CRP, IP-10 and TNF-related apoptosis-inducing ligand (TRAIL); FebriDxTM (RPS Diagnostics, Sarasota, FL, USA), a rapid semi-quantitative test combining CRP and the myxovirus resistance protein 1 (MxA), a marker for viral infection; SeptiCyte® (Immunexpress, Seattle, WA, USA) which uses reverse-transcription, PCR to quantify four host response genes and the PSP IVD capsule for the abioSCOPE® (Abionic, Epalinges, Switzerland) (Sambursky, Shapiro 2015, Escadafal, Nsanzabana 2017).

Time will tell whether these tests ultimately fulfil their theoretical diagnostic potential in children with suspected pneumonia in LMICs or whether cost, time to process preclude their introduction and attention turns to more readily available markers.

Chapter 6

Case management

The WHO summarised the advantages of the new recommendations as follows (WHO 2014)

- ´Oral amoxicillin can be used to treat both fast breathing pneumonia and chest indrawing pneumonia
- Pneumonia classification and management are simplified to two categories
- Access to antibiotic treatment closer to home is increased.
- The need for referrals to higher level facilities is decreased.
- Reduced risk of nosocomial and injection borne diseases is reduced.
- The probability of antimicrobial resistance is diminished
- Training of health workers is simplified.

Specific treatment regimes for children aged 2-59 months have been recently simplified in line with the reclassification´.

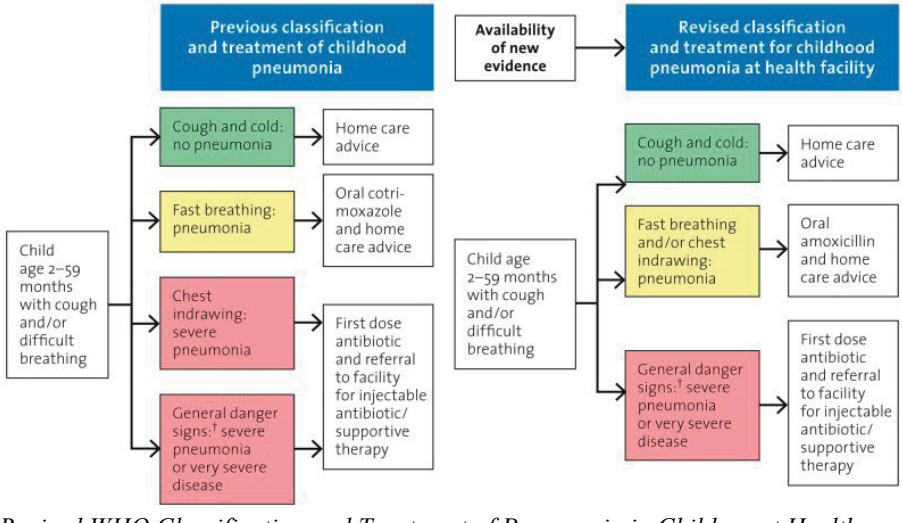
Detailed recommendations are as follows

1. Children with fast breathing (previously non-severe) pneumonia with no chest indrawing or general danger sign should be treated with oral amoxicillin (40mg/kg/dose twice daily) for 3 days in low HIV prevalence areas and 5 days in other areas.

Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should be referred to a facility able to provide second-line treatment.

2. Children with chest indrawing pneumonia should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily for five days.
3. Children with severe pneumonia (both HIV negative and positive) should be treated with parenteral ampicillin (or penicillin) and gentamicin for 5 days using the following doses: ampicillin: 50 mg/kg; benzyl penicillin: 50 000 units per kg IM/IV every 6 hours; gentamicin: 7.5 mg/kg IM/IV once a day.

4. Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.
5. Empiric cotrimoxazole treatment for suspected Pneumocystis jirovecii (previously Pneumocystis carinii) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia. However, empirical cotrimoxazole treatment for Pneumocystis jirovecii pneumonia (PCP) is not recommended for HIV-infected and exposed children over 1 year of age with chest indrawing or severe pneumonia.



Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries.

Geneva: World Health Organization; 2014.

Oxygen

Hypoxaemia resulting in hypoxia (poor tissue oxygenation which often follows) is a major cause of pneumonia-related mortality. Oxygen is on the WHO essential medicines list and, though there is some controversy around appropriate cut offs for treatment, most would agree it should be used where saturation is below 90% in air irrespective of altitude. There are a number of affordable saturation monitors and means of delivering oxygen, for example cylinders and concentrators. What is unacceptable, though still prevalent, is a

situation in which hypoxia is detected, but, the means to deliver oxygen (in other words, treat) unavailable (Duke, Graham et al 2010).

Many children will be hypoxaemic and, most of those who are, also hypoxic. They require early respiratory support, but may have few or no clinical signs other than a low saturation (Colbourn, King et al 2020). Secondary care admission is recommended in part to monitor for and enhance earlier intervention in the case of deterioration and partly in order for reassessment by experienced physicians to rule out alternative pathology (Agweyu, Lilford et al 2018).

In the past, the patchy literature resulted in a lack of clarity around saturation monitoring and outcome in terms of mortality (Enoch, English 2015). The benefits are now, however starting to become clearer. A recent estimate (Floyd, Wu et al (2015)) of the potential of saturation monitoring coupled with treatment if appropriate showed both good discriminatory property between severe and non-severe pneumonia, and the potential to save up to 148,000 lives per year. More recently still, Colbourn demonstrated the additional discriminatory power through baseline saturation measurement and early referral (Colbourn, King et al 2020).

Measurement of oxygen saturation improves prediction of severity and (the evidence suggests) should be, but is not yet, widely available. There is evidence from qualitative stakeholder data from Malawi, Sudan, Ethiopia, Cambodia and Uganda that fingertip devices and the acute respiratory infection timer are acceptable especially those not dependent on an uninterrupted electricity supply (King, Boyd et al 2018, Spence, Baker et al 2017).

There are a number of initiatives to improve distribution and affordability of saturation monitors including ‘Lifebox’, a low-cost, reusable robust, portable, battery-operated oximeter which can be used with standard boxes (for example Massimo) or the Lifebox equivalent as well as smartphone interpreted devices. These are both acceptable and have a performance in terms of time to first plausible saturation reading comparable to more expensive counterparts Boyd showed that plausible values were achieved in 67% in < 1 minute, and 90 % in < 5 minutes. Performance improved with age: using neontates as the reference group, infant adjusted odds ratio [aOR] was 1.87 (95% confidence interval [CI]: 1.16, 3.02) : in toddlers aOR: 4.33 (95% CI: 2.36, 7.97) and in children aOR; 3.90, 95% CI: 1.73, 8.81). 70% and 63% of readings being made within a minute using the Life- box probe and the Massimo or Lifebox box respectively (Boyd, King 2018 et al).

Advances in management

The primary purpose of guideline-based treatment is the reduction in mortality. As such, treatment thresholds are low, but this in itself is controversial, substantial recent debate generated by the perceived need or not of any treatment other than supportive. I will return to this theme in the 'controversies' section. Though a thorough examination of new innovations is beyond the scope of this thesis, the following areas (all with exciting potential) deserve mention.

Global action plan for pneumonia and diarrhoea.

- The WHO and UNICEF integrated Global action plan for pneumonia and diarrhoea (GAPPD) (WHO, UNICEF 2015) aims to accelerate pneumonia control with a combination of interventions. The underpinning philosophies include:
- Protection of children by promoting exclusive breastfeeding and adequate complementary feeding.
- Prevention of pneumonia with vaccinations, hand washing with soap, reducing household air pollution, HIV prevention and cotrimoxazole prophylaxis for HIV-infected and exposed children.
- Treatment by ensuring all children have access to the right kind of care (community health worker or, if severe, a health facility) and can get antibiotics and, if required, oxygen.

Mhealth

Mhealth is the generic term for the use of mobile technology in improving case management in health. Early exploration of the potential in pneumonia in children though android applications, suggest that it can enhance health worker estimation of observations such as respiratory rate and oxygen saturation and improve adherence to risk classification and IMCI based treatment algorithms (Ginsburg, Delarosa 2015, Mhealth might additionally, have a role in early detection of pneumonia in children in high risk households: one such programme (currently under trial) is the Pakistan pneumonia perception project, an early detection algorithm run by the key children's primary health contacts, the Lady Health Workers (https://ichgcp.net/clinical-trials-regis- try/NCT03756259).

Algorithmic enhancement

There are a bewildering number of predictive algorithms besides the non-specific WHO trigger score system for use by health workers which relies largely on a syndromal approach (based heavily on respiratory rate) to rule in

or out pneumonia. These Paediatric Early Warning (PEWS) Scores using either triggers or composite thresholds have proliferated though evidence of efficacy in terms of reducing in hospital mortality is controversial. The recent EPOCH cluster trial randomizing European paediatric emergency departments to an early warning score the 'bedside PEWS' in addition to standard care or standard care alone study included 21 hospitals in 7 countries (Belgium, Canada, England, Ireland, Italy, New Zealand, and the Netherlands) and 144,000 children (Parshuram, Dryden-Palmer et al 2018). There was no evidence of a reduction in mortality in children additionally triaged with the PEWS. There was, though, an effect on predicting deterioration, and this area, early warning is where the tools might be of most use in the future (Chapman, Wray et al 2019).

A new score, the POPS (Paediatric Observation Priority Score) already widely used in the UK uses a philosophically similar nuanced approach to standard physiological parameters. The additional measures are work of breathing, past medical history and, thought provokingly, the triaging nurses´ gut feeling. It has both good predictive value and, interrater reliability. (Langton, Bonfield et al 2018).

With this recognition, attention at the WHO has turned to enhancing the predictive performance of the screening tools by augmenting the traditional algorithmic cut offs with additional, readily measurable parameters such as fever and modifications to age adjusted respiratory rates. Recent analysis by the WHO of data from 138,000 episodes and 4,000 deaths led to the establishment of an algorithm group and potential revisions currently being tested in Africa and Asia. (WHO 2018).

It is not yet known whether other measures of physiological compromise such as lactate, pH, pCO2 (readily obtained from a bedside capillary blood gas) will augment the predictive value of the clinical scores in the future. Though essentially point of care (POC) tests, the analysers are expensive and unwieldy and not an option in primary (often not even in secondary) care settings in LMICs.

Preventing chronic morbidity

Attention has now moved to the prevention of chronic morbidity including: enhancing recovery, reducing mortality, the identification of children needing admission and oxygen and optimal antibiotic choices and duration and the prevention of complications, for and nutritional rehabilitation (Chang, Ooi 2013, White Johanson, Nsona et al 2017).

Chapter 7

Prevention

Poverty

Childhood pneumonia is intimately linked to poverty in all its manifestations. These include parental education, overcrowding, undernutrition, incomplete vaccination and the use of indoor fossil fuels (Scott, Brooks et al 2008, Niessen, ten Hove et al 2009). The relative contribution of each is hard to ascertain epidemiologically as there is substantial collinearity between each of the fac- tors and the others (Rudan, O'Brien et al 2013) but have all been shown to be independent predictors. Overcrowding alone has an estimated Odds Ratio (OR) of 2.15 (95% CI 1.46- 3.18) (Foncesca Lima, Goncalves Mello et al 2016).

Undernutrition

Leung and Chisti summarised the now unequivocal effects of undernutrition. Their systematic review showed that severe malnutrition predicted death even after hospital discharge and that nutritional rehabilitation reduces case fatality rates. Additionally, exclusive breastfeeding of infants reduces deaths due to both pneumonia and diarrhea especially in the first 6 months of life (Leung, Chisti et al 2016).

Indoor air pollution

Indoor air pollution (IAP) in the form of fine particulate matter (for example from solid fuel cooking) and tobacco have been shown in many settings to predict both asthma and pneumonia. The main environmental culprits are NO2, ozone (O3), fine particulate matter (PM 10 and PM 2.5) and, of course tobacco smoke (Bouazza , Foissac et al 2017, Been and Sheikh 2018). Dose response relationships to each of these demonstrate the potential for control measures and Niessen estimated that solid fuel use contributes 30% (95% CI 18-44%) to pneumonia burden (Niessen, ten Hove et al 2009). IAP is, however, complex, the particulate matter alone being derived from a wide range of sources - burning dung, crop residues, wood and charcoal, spores and pollen. In a systematic review of the effects of IAP on respiratory health, Adaji

found no effect of carbon monoxide alone, but a consistent adverse effect of particulate matter of PM2.5 when measured by solid fuel use though not when directly measured. (Adaji, Ekezie et al 2019).

Two randomized trials (Malawi and Guatemala) of improved, lower biomass dense interventions showed little effect on primary pneumonia outcome but some effect on reducing exposure concentration (Mortimer, Ndamala et al 2017 and Smith, McCracken et al 2011) and the time might have come to look beyond indoor to outdoor pollution.

Vaccination

Vaccination against haemophilus b and s. pneumonia has transformed the landscape over the last decade. Recent WHO and maternal and child epidemiology collaboration work suggested that pneumococcal deaths declined by 51% and Hib deaths by 90% from 2000 to 2015 (Wahl, O'Brien et al 2018). Surveillanceo data on children receiving three doses of Haemophilus B vaccination has demonstrated a reduction in pneumonia incidence of 62% to 70% among Pakistani children (Khowaja, Mohdiuddin et al. 2013) Most children who died of pneumococcus (81%) and Hib (76%) presented with pneumonia. Despite widespread vaccination, there were an estimated 3•7 million episodes of severe pneumococcal and 340 000 episodes of severe Hib globally in children in 2015.

It is clear that the widespread use of Hib vaccine and the recent introduction of PCV in countries with high child mortality are associated with reductions in Hib and pneumococcal cases and deaths. This might well improve further as the serotype range in PCV expands, but further progress towards further reducing the global burden of Hib and pneumococcal disease burden will depend on the efforts of a few pivotal Asian and African countries.

Antibiotic stewardship

As discussed in Chapter 2, another area with great potential is that of antibiotic stewardship. The issues can be summarized as: limiting treatment to those children who need it, for the shortest period possible. This requires change on several levels: surveillance and accessibility (limiting over the counter availability) and raising awareness of the self-limiting nature of the majority of respiratory tract infections amongst clinicians and parents (Phuong, Huang et al 2017).

Horizontal programmes.

As discussed in the epidemiology chapter, more recent approaches have involved collaborative 'packages', a composite of strategies to tackle the commonest predictors and the use of composite databases such as the Global

Antibiotic Resistance Program (GARP), the Center for Disease Dynamics, Economics and Policy (CDEP 2018) and the WHO Global Antibiotic Resistance, Use Surveillance System ('GLASS')

Another spoke has been the multicentric epidemiological surveillance groups which have informed targeting. These include: CHERG (the child health epidemiology reference group); PERCH (pneumonia etiology research for child health) and GABRIEL (Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income Countries) (Leung DT, Chisti MJ et al 2016).

Another strand, launched by the WHO and UNICEF in 2013, the Global Action Plan for Prevention of Pneumonia and Diarrhoea (or GAPPD) approach aims to roll out primary prevention of the common risk factors of both pneumonia of diarrhoeal illness (Bhutta, Das et al 2013). These include: the promotion of universal breastfeeding for the first 6 months; universal vaccination coverage; access to oral rehydration; appropriate care seeking for pneumonia; access to clean water for handwashing and drinking and appropriate sanitation and the use of non-pollutant household fuel (WHO, UNICEF 2013). Many consider this approach, a horizontal rather than vertical ('silo'-type) to be the best hope for progress long term (Rudan, O'Brien et al 2016, Niessen, ten Hove 2009, Scott, Brooks et al 2008). The initiative 'Every Breath Counts' (https://stoppneumonia.org) is a good example of this broader ultimately more sustainable approach.

Chapter 8

Economic costs of child pneumonia

The detailed health economic aspects of pneumonia are beyond the scope of this thesis, but, some reference to work in the area is, nonetheless, justified as societal and family costs are considerable.

Zhang's review of 34 studies included data on more than 95 000 children with pneumonia from both LMICs and high–income countries (HIC). The total cost (per episode) for management of severe pneumonia was US$ 4.3 (95% CI 1.5–8.7) in community settings, US$ 51.7 (95% CI 17.4– 91.0) in outpatient settings and US$ 242.7 (95% CI 153.6–341.4)–559.4 (95% CI 268.9–886.3) in hospital in–patient settings in LMICs. Mean inpatient duration for severe episodes were 5.8 days (IQR 5.3-6.4) and direct care sums translate to between 26.6% and 115.8% of patients' monthly household income. (Zhang, Sammon et al 2016).

Investment in vaccination and other preventative programmes in unequivocally worthwhile. Mason and Chopra estimated in 2013 that scaling up of existing interventions against pneumonia and diarrhoea to 80 and immunisation to 90% would eliminate more than two-thirds of deaths at a cost of US $ 6•715 billion by 2025. Their model suggested that all countries made progress at the same rate as the respective regional leaders, then cause-specific death rates of fewer than three deaths per 1000 livebirths from pneumonia and less than one death per 1000 livebirths from diarrhoea could be achieved by 2025 (Chopra, Mason 2013).

Further work on the cost effectiveness of preventative measures by Niessen, showed that programmes including community treatment, breastfeeding promotion, zinc supplementation and haemophilus B and pneumococcal vaccination had cost effectiveness ratios of 10-60 international $ and < 120 I$ per Disability Adjusted Life Year (DALY) in LMICs and MICs respectively (Niessen, ten Hove et al 2009).

Chapter 9

Ongoing controversies central to the studies: prevention, identification and case management

The original research in this thesis examines four areas in childhood pneumonia in LMICs all of which have been alluded to and discussed in earlier sections.

Three of these have implications for individual case management: severity scoring and triage; antibiotic treatment in fast breathing (previously non-severe) pneumonia and the place of adjunctive zinc treatment. The fourth is primarily of importance at a population level and estimates the burden of recur- rent pneumonia predicted by indoor air pollution which has implications for targeted public health measures.

Each area, despite existing literature, continues to be debated and each question required different approaches in terms of hypothesis, design and analysis to the others.

Controversy 1

Case management

Are antibiotics still required in children in South Asia with fast breathing pneumonia? (Papers 1 and 2)

Pneumonia is a major cause of child morbidity and mortality in low resource countries (Boloursaz, Lotfian et al. 2013). Though there is a wide spectrum of severity and aetiology, the WHO has, until now, recommended empiric antibiotic treatment prescription guidelines to cover bacterial infection (World Health Organisation, Geneva 2012). Given the change in epidemiology in the post pneumococcal and haemophilus B vaccination era, this broad recommendation for empiric antibiotic use in all children with pneumonia, including those with isolated fast breathing (previously 'non-severe' pneumonia), has been questioned (Fox, Baqui et al. 2015, Awasthi, Garwal et al. 2008, Hazir, Nisar et al. 2011, Mulholland, Carlin et al. 2014, Mulholland, Carlin et al 2015). We know that a far smaller proportion of children presenting with the fast breathing phenotype have bacterial pneumonia than a

decade ago and the majority now have more largely benign self-limiting viral pneumonia (Boloursaz, Lotfian et al. 2013, Levine, O'Brien et al. 2006, Cowgill, Ndiritu et al. 2006). In Pakistan, the Hib vaccine was introduced in the universal immunization program in 2009 and pneumococcal conjugate vaccine in 2013-14. Surveillance data on children receiving three doses of Haemophilus B vaccination has demonstrated a reduction in pneumonia incidence of 62%–70% among Pakistani children. (Khowaja, Mohdiuddin et al. 2013).

Children with 'fast breathing pneumonia' (until 2014 classified by the WHO as "non-severe pneumonia") have a generally mild illness, of which up to 65% of cases are viral (Levine, O'Brien et al. 2006) with many of the remainder having self-limiting bacterial infection (Ruuskanen, Lahti et al. 2011). In short, spontaneous recovery is common and may render antibiotics redundant and potentially harmful. The risk of harm from unnecessary antibiotic use is twofold: individual and population level. At the individual level, side effects to antibiotics, both unpleasant and dangerous, must be considered as well, potentially as expense for the family. Frequent exposure to antibiotics has also been shown to have long-term deleterious effects on the native gut microbiota that may impair growth and nutrition in children (Penders, Thijs et al 2006). As a result of this, there may be altered immune processing resulting in long- term risk of subsequent infections (Bailey 2012, Buffie, Jarchum et al. 2011, Wilks and Golovkina 2012). At a public health population-based level, there is the risk of potential emergence of resistance of common pathogens to first line antibiotics and the need to use more expensive (sometimes more toxic), harder to administer alternatives (Kritinsson 1997, Uzuner, Ilki et al. 2007, Woolfson, Huebner et al. 1997). Infections due to antibiotic resistant pathogens not only make people ill for longer but also unnecessarily burden health care resources and increase cost (World Health Organisation 2018). The cost of antibiotic treatment for all children with WHO-defined pneumonia is formidable. Antibiotic treatment for all children with pneumonia in South Asia & sub-Saharan Africa costs an estimated $ 200 million (Edejr, Aikins et al. 2005). In Pakistan, the average cost to treat one episode of pneumonia in a child as an outpatient was estimated to be US$ 13.44 in 2006, representing 82% of annual health expenditure per person at that time (Hussain, Waters et al. 2006).

Unnecessary antibiotic prescription is a major contributor to antibiotic resistance and puts a strain on individuals and under-resourced programs in low- income countries. This crisis has arisen largely as a result of increased antibiotic use with the predictable consequence of microbial mutation to the point that, in some settings, many previously pan-susceptible organisms are now almost untreatable even with third generation cephalosporins and carbapenems. The problem is particularly acute in South Asia. A recent systematic review of etiology in developing countries of infant sepsis aged 1

to 12 months with no clear focus of infection in developing countries has shown in vitro susceptibility to chloramphenicol/penicillin, penicillin/gentamicin, and third generation cephalosporin of only 47%, 63%, and 64%, respectively (Downie, Armiento et al. 2013). These issues must, however, all be placed into the context of adequate identification of those children who are or who are likely to deteriorate. This requires discriminatory screening tools, none of the current candidates showing the hoped for performance (Deardorff KV, McCollum ED 2018).

The last comprehensive Cochrane review looking at use of antibiotics in pneumonia in 2009 including 27 trials did not identify any studies comparing antibiotic with placebo (Kabra, Lodha et al. 2013). Another in 2014 specifically assessing standard versus no antibiotic therapy in children with non-severe pneumonia and wheeze did not find a single study, meeting inclusion criteria and concluded that randomized controlled trials in appropriate populations were required (Lassi, Kumar et al. 2014).

However, two recent randomized controlled trials (RCTs) in South Asia and one in Africa give us some information. Hazir et al. conducted a double-blinded RCT of oral amoxicillin versus placebo for non-severe pneumonia in four centers in Pakistan, using age-dependent WHO cut-offs for dosing. Cumulative treatment failure (TF) by day 3 was similar in both groups: 7.2% (31/431) of children in the amoxicillin group and 8.3% (37/442) in the placebo group as were rates of relapse between by day 14. There were no deaths. The second randomized placebo controlled multicentre trial was conducted in India in out-patient clinics associated with tertiary care hospitals (Awasthi, Garwal et al. 2008). This trial used the WHO criteria for non-severe pneumonia, but only enrolled children with wheeze (audible or auscultatory). Treatment failure was defined as development of WHO-defined severe or very severe pneumonia, hypoxaemia (SpO2 < 90%), fever (temperature >1010F) or persistence of non-severe pneumonia, or wheeze. Relative failure rates were 24.0% (201/836) in the placebo group and 19.9% (166/835) in the amoxycillin group, a rate difference just significant at 4.2% (95% CI 0.2 to 8.2), but, with no difference in the rates of relapse.

More recently (2016-17) Ginsburg et al. conducted a randomised controlled trial in Malawi, Southern Africa, testing non-inferiority of placebo against amoxicillin in non-HIV infected children with fast breathing pneumonia (Ginsburg 2018). This study began at approximately the same time as RETAPP, but, as a result of significant differences in failure rates (though no deaths) at an interim analysis (7.0% placebo vs 4.0% amoxicillin) was terminated early. It is unclear whether these findings can be generalised to other LMIC settings, given inherent likely genetic and epigenetic nutritional, metabolic and immunological differences.

The South Asian studies were conducted before Hib and pneumococcal vaccines were introduced in the local setting and, until now there has been no high quality evidence to guide the management of children with fast breathing

pneumonia with bronchodilator unresponsive wheeze in community settings in Asia, the WHO calling for trials to inform guidelines (Biswas, Carty 2012). Our non-inferiority trial tests the Null hypothesis of inferiority of placebo against standard antibiotic treatment in children 2 to 59 months of age in poor urban slum settings in Karachi, Pakistan with an established PCV and HIB vaccination programme.

The 'RETAPP' (Randomised Equivalence Trial of Antibiotics in Pediatric Pneumonia, NCT02372461), a double blinded randomized controlled trial, tested the hypothesis that the absolute treatment failure rate of children 2–59 months of age presenting at a primary healthcare (PHC) facility for treatment of WHO defined fast breathing pneumonia who receive 3 days of placebo is not worse than 3 days of amoxicillin by 2.5% (TF placebo—TF amoxicillin >2.5%, assuming TF of 5% in amoxicillin group). Couched differently, the trial assessed whether children aged 2 to 59 months of age with WHO-defined fast breathing pneumonia presenting at a PHC facility in a poor peri-urban setting assigned placebo (highly prevalent undernutrition and complete PCV vaccination of around 50%) have higher failure rates than those assigned three days of oral amoxicillin (Jehan F, Nisar I et al, 2019). The Null hypothesis is of inferiority of placebo. Secondary analyses will explore the proportion of children with fast breathing pneumonia who have pneumococcal carriage, viral carriage or both in nasopharyngeal specimens and to evaluate predictors of treatment failure (TF) with regards to viral or bacterial nasopharyngeal carriage.

Outline of procedures: Randomised trial of antibiotics in pediatric pneumonia (RETAPP): NCT02372461

Study setting: Four primary healthcare centers (PHC) located in low-income communities in Bin Qasim town, a large, coastal peri-urban slum area of Karachi under health and demographic surveillance by the Department of Child Health, Aga Khan University, Karachi.

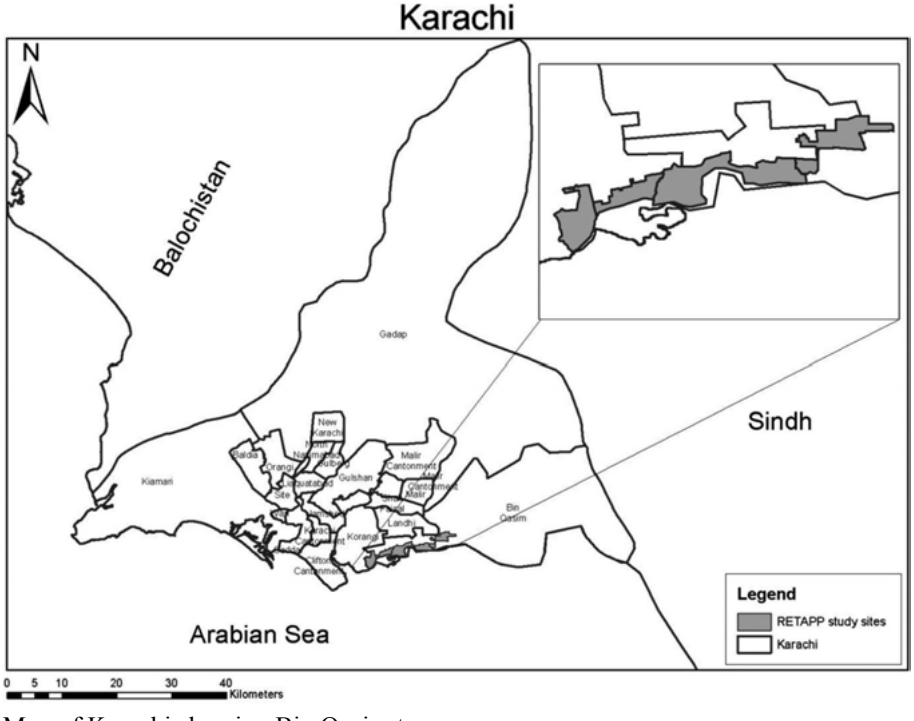
Children in the reference arm received the WHO regimen of oral Amoxicillin in two divided doses for three days using WHO Integrated Management of Childhood Illnesses (IMCI) recommended weight bands (World Health Organisation. 2016). Children in the comparison arm received pharmacologically inert placebo similar in appearance in two divided doses for three days. Recruitment and follow-up: Children between 2 to 59 months old with cough or difficult breathing, presenting at the participating PHCs were screened for eligibility by the study physicians. If eligible the parent/guardian was referred to an independent physician to obtain written informed consent. If consent was given, the child was enrolled then randomized using a serial identification number will be assigned.

All enrolled children received a study drug by CHW in accordance with the randomization number in morning and evening on day 0, 1 and 2. Children were followed for compliance and out- come twice daily on days 0, 1, 2, 3, with a morning assessment by a study physician in the study clinic and a home

visit in the evening by a CHW. Subsequently, children were seen by a study physician once on days 5, 14 and 21. At follow-up visits participants were examined by study physician in the morning and CHW in the evening for resolution of high respiratory rate along with signs of treatment failure and relapse (Fig. 2). All adverse events were recorded on the adverse event reporting form (AERF). The schedule of follow- up is derived from our experience of a trial in younger infants [27] and taking into consideration safety of the enrolled children.

Blinding and randomisation: Randomisation was undertaken in blocks of varying sizes (4, 6, 8 and 109 to prevent prediction of next assignment and to ensure sequence allocation concealment. Random sequence lists were stratified by age group (2–11 months and 12–59 months) to maintain similar composition of ages in both study arms and drug labels (antibiotic or placebo) generated in order to reduce the chance that prescription errors would occur as a result of the use of different weight bands for antibiotic dosages in the respective age groups.

The study was be monitored by both an international steering committee and data monitoring committee, neither with direct involvement with the trial.



Map of Karachi showing Bin Qasim town

Controversy 2

Indoor air pollution and recurrent fast breathing (paper 3)

Childhood pneumonia is intimately linked to poverty in all its manifestations. These include overcrowding, undernutrition, incomplete vaccination and (in some studies outside Asia) the presence of indoor air pollution (IAP) (Scott, Brooks et al 2008, Niessen, ten Hove et al 2009, Sonego, Pellegrini et al 2015, Adaji, Ekezie et al 2019).

Sonego's meta-analysis estimated effect sizes for a range of socio-economic predictors and found that early pneumonia mortality was significantly related to: young maternal age adjusted OR (aOR) 1.84 (95% C, 1.03–3.31); low maternal education aOR 1.43 (1.13–1.82); low socio-economic status aOR 1.62 (1.32–2.00); second-hand smoke exposure aOR 1.52 (1.20 to 1.93); IAP aOR 3.02 (2.11–4.31). Protective factors included: immunisation aOR 0.46 (0.36–0.58) and good ante- natal practices aOR 0.50, 0.31–0.81 (Sonego, Pellegrini et al 2015).

Leung and Chisti summarised the now unequivocal effects of undernutrition. Their systematic review showed that severe malnutrition predicted death pneumonia case load and death even after hospital discharge and that nutritional rehabilitation reduces case fatality rates. There is additionally, extensive and consistent literature about the benefits of exclusive breastfeeding of infants in the reduction of deaths from both pneumonia and diarrhea especially in the first 6 months of life (Leung, Chisti et al 2016). Another potentially modifiable environmental factor is household overcrowding: again the literature is broad and compatible: Foncesca Lima, for example, estimated the effect size as aOR of 2.15 (95% CI 1.46- 3.18) (Foncesca Lima, Goncalves Mello et al 2016).

The relative contribution of each airborne pollutant is arguably harder to ascertain epidemiologically as each of the factors, black carbon, fossil fuel, fine particulate matter (PM 2.5) and carbon monoxide (CO), are so closely linked to all the others (Rudan, O'Brien et al 2013). Extrapolating this, Adaji's meta-analysis showed no association between home CO exposure and pneumonia. Fine particulate matter was only significant when using fuel as a proxy for exposure and not when measured directly highlighting the issues with standardizing exposure measurement in such settings (Adaji, Ekezie et al).

Indoor air pollution in the form of fine particulate matter, for example, from solid fuel cooking (itself a heterogenous entity) and tobacco have been shown in many settings to predict both asthma and pneumonia (Sonego, Pellegrini et al 2015, Adaji, Ekezie et al 2019, Been and Sheikh A 2018, Bouazza, Foissac et al 2017). The main environmental culprits are NO2, ozone (O3), fine particulate matter (PM 10 and PM 2.5) and, of course tobacco smoke (13, 14, 15,16). Dose response relationships to each of these demonstrate the potential

for control measures. Niessen estimated that solid fuel use contributes 30% (95% CI 18-44%) to pneumonia burden (Niessen, ten Hove et al 2009).

The area of IAP, though, despite hypothetically modifiable predictors, remains controversial. There is now randomized controlled trial evidence suggesting that reducing household particulate matter might not be the sole solution.

Two randomized trials (Malawi and Guatemala) of improved, lower biomass dense interventions (fuel and Plancha stoves) showed little effect on pri mary pneumonia outcome except in severe pneumonia in the Guatemala trial but some effect on reducing exposure concentration (Mortimer, Ndamala et al 2017 and Smith, McCracken et al 2011).

In Mexican women, Romieu, however, despite poor adherence found the Patsari stove reduced respiratory symptoms (rate ratio [0•29 [95% CI 0•11–0•77] for wheeze) and lung function decline (31 mL vs 62 mL over 1 year; p=0•01) in those who used the stove. (Romieu, Riojas-Rodríguez et al).

Though there is some literature on environmental predictors of recurrent pneumonia, there is very little to date from Asia and almost none from Pakistan, a knowledge gap this study aimed to address.

To explore this further, we undertook a nested case control study couched within the 'RETAPP' trial (Brown, Rizvi, Kerai et al 2020). As described in the preceding section, RETAPP was a double blinded, randomized controlled trial testing the hypothesis that treatment failure rates in children with fast breathing pneumonia will be non-inferior in children given a placebo to those treated with standard WHO treatment of oral amoxycillin. The primary outcome is a composite treatment failure 3 days after randomization. At enrolment, detailed socio demographic data including IAP exposure was obtained on every child.

All participants in RETAPP were eligible for inclusion in the 'recurrent fast breathing' nested case control study. A case was defined as a child previously randomised in RETAPP who re-presented with a recurrent episode of isolated fast breathing be- tween eight weeks to one year of the initial episode. Eight weeks was considered a sufficient wash-out period for resolution of prior episode of fast breathing and the endpoint of a year was chosen for consistency with hospital studies of recurrent pneumonia. Controls were defined as children between 2-59 months of age, enrolled in the RETAPP trial and who did not present with a recurrent episode of fast breathing during the defined time period.

Children fulfilling the eligibility criteria of case and control described above were flagged in RETAPP database of enrolled children. For case selection children enrolled in RETAPP, who presented again with a recurrent fast breathing episode, were identified through their DSS identification number, date of birth and first name. Children with missing or incorrectly recorded identification numbers or non-matching date of birth of birth or first

names between first and second visit were excluded. For control selection, a list of enrolled children who had not re-presented with fast breathing was generated from trial data. To adjust for confounding by age (given the association with both pneumonia incidence and vaccination completeness), each case was matched by age to two controls

The outcome variable was the risk by exposure category (IAP +/-) based on a cut off determined by principle component analysis for the recurrence of fast breathing. The sample size estimation was based on an OR of 2.5, a level at which public health importance was considered likely.

Data was extracted for both cases and controls on several possible candidate predictors for fast breathing recurrence including age, sex, siblings, number of people reported to sleep in same room, exclusive breast feeding (up to six months of age), duration of pregnancy (full term, preterm), type of housing (based on material of roof, wall and floor), WASH status (water and sanitation), nutrition status (based on Z-scores of height for age, weight for age and weight for length), maternal and paternal education (never or ever been to school), presence of pet animal in house, fever, oxygen saturation and wheeze (auscultation by physician) from their baseline case recording at the time of enrollment in the trial. Information on vaccination status (complete, incomplete or not vaccinated according to age and schedule provided by Expanded Program on Immunization) and air quality index was also collected. An indoor air quality index was created from six variables reflecting indoor air pollution (ventilation, passive smoking, type of fuel and stove, cooking place and presence of child near cooking area) using principal component analysis (PCA). Quartiles were further created from PCA score to group sample population into three categories: good, moderate and poor, indicating indoor air pollution gradient. (PCA on air quality ref).

The strength of association between candidate environmental predictors was estimated in a multivariable logistic regression model and public health implications for significant associations evaluated.

Controversy 3

The role of adjunctive zinc treatment in severe pneumonia (paper 4)

Background

Standard treatment of severe pneumonia is comprised of adequate hydration (oral, nasogastric or intravenous), broad spectrum antibiotics appropriate to local microbiological epidemiology and oxygen where hypoxaemia is detected. The now widely available saturation monitors have enhanced detection of hypoxia, but, without the facility to treat with supplemental oxygen (and the best mode is controversial) have little influence on pneumonia- related mortality (WHO 2014, Enoch, English et al 2014).

Micronutrients and their relation to pneumonia have been the subject of research interest for many years. Most would now agree that on the key findings in Vitamin A research: that neonatal supplementation in areas of population deficiency reduces subsequent total mortality (WHO Vitamin A group 2018) but, in pneumonia does not alter disease trajectory (Brown, Roberts 2004).

The role of zinc, another key micronutrient, however, remains controversial. It functions as an immune modulator, deficiency resulting in increased susceptibility to infection as well as impairing growth and development (Krebs, Miller et al 2014). Zinc supplementation as an adjunct to standard re-hydration enhances recovery from acute gastroenteritis in LMICs and in meta-analysis reduces mortality by an estimated 23% (Fischer-Walker, Black et al 2010). Population preventative supplementation also reduces all cause mortality (Yakoob, Theodoratou et al 2011) and reduces pneumonia incidence at least in young children if administered regularly (Lassi, Moin et al 2016, Roth, Richard et al 2010).

The role of adjunctive zinc at presentation in pneumonia is more controversial: meta analyses published in 2011, 2012 and 2016 (Haider, Lassi et al 2011, Das, Singh et al 2012, Tie, Tan et al 2016) found no effect, while another published in 2018 estimated a significant reduction in mortality (RR 0.43 95% CI 0.22 to 0.83) but no difference in composite treatment failure rates (Wang, Song 2018).

As this area of research remains active and because fundamental public health questions have not yet been fully answered, we undertook a systematic review and meta-analysis of randomized controlled trials in which children with pneumonia in LMICs were assigned to zinc or placebo as adjunctive treatment. The main outcomes of interest were treatment failure, death and adverse effects each assessed by a pooled Odds Ratio or proportional hazards. Studies were assessed for quality and risk of bias using a priori rules. Synthesis was undertaken with a random effects approach. The meta-analysis was registered in advance on the PROSPERO database for systematic reviews.

Controversy 4

Predictive value of a respiratory risk score in the emergency department of a Low and Middle Income country (paper 5)

Acute respiratory illnesses both infective and inflammatory are major contributors to the global burden of child disease (WHO 2014). The prevalence of asthma is 10%, and acute respiratory infection is the single largest contributor to under 5-year-old mortality (Khan, Tanzil et al 2014, WHO 2014, Eder, Ege et al 2006) and the burden in Pakistan substantial (Atiq, Siddiqi 2015).

Diversity in clinical presentation of paediatric respiratory distress warrants a uniform approach to evaluation and management. There are, however, a bewildering number of predictive algorithms besides the non-specific WHO trigger score system for use by health workers which relies largely on a syndromal approach (based heavily on respiratory rate) to rule in or out pneumonia. The majority of paediatric respiratory scores aim either to differentiate upper and lower tract illness or are age specific (Ducharme, van der Windt 2000, Smith, Baty et al 2002).

Rather than simplify the science of early warning scores, the proliferation in tools since the first wave in the 1990s has probably complicated choice and shown their individual limitations. There are two broad types: the trigger tool and the score. The former depends on a predetermined threshold in one physiological parameter (for example heart rate) being 'passed' (exceeded) and is probably easier to administer while the latter uses a total score system. Both are subject to individual error and inter observer variation. Given the lack of evidence for their effectiveness at least on mortality (Chapman, Wray et al 2018), the number of scoring systems (33 in a recent review) is extraordinary (Chapman and Wray 2019).

The recent EPOCH cluster trial randomizing European paediatric emergency departments to an early warning score the 'bedside PEWS' in addition to standard care or standard care alone study included 144,000 children: it found no evidence of a reduction in mortality in children additionally triaged with the PEWS. More promisingly, however, there was an effect on early recognition of deterioration (Parshuram, Dryden-Palmer et al 2018).

A new score, the POPS (Paediatric Observation Priority Score) already widely used in the UK uses a philosophically similar nuanced approach to standard physiological parameters. The additional measures are work of breathing, past medical history and, unlike other scoring systems, the triaging nurses' gut feeling. It has good predictive value and, very importantly from an individual patient trajectory good interrater reliability (Langton, Bonfield et al 2018).

With this recognition, attention at the WHO has turned to augmenting the traditional algorithmic cut offs with extra predictive information such as fever and modifications to age adjusted respiratory rates.

In addition, there is now an appreciation that the tools are, to some extent, context dependent and reflect the clinical environment (and human error) in which they are used (Chapman and Peters 2019). The time feels right to focus on modifying settings and procedural infrastructure.

What then are the prerequisites for a risk score in the paediatric emergency department in a Low and Middle Income Country? Factors that need to be considered are workload, training and acceptability as well as discriminatory power in the recognition of children likely to require intensive care. The

Clinical Respiratory Score (CRS) is attractive for several reasons: it is comprised of a number of predictors of respiratory distress, for example, child's colour, respiratory rate, presence of wheeze, use of accessory muscles, mental status and oxygen saturation (Crabtree, Mariscalco et al 2011, Meyers, Shook et al 1996). It requires minimal resources and is therefore well suited to LMIC set- tings. It was first introduced and tested in a high-income country setting in over 300 patients, aged 1 to 18 years, who presented to the ED with symptoms that suggested reactive airway disease/ asthma and was the further validated for acute chest syndrome presentation in sickle cell disease patients in the US). The CRS, however, has not until now been validated in LMICs, for respiratory distress presentations either from primary respiratory or non-respiratory illnesses. Unlike the multiple alternatives, the CRS includes parameters that might allow it to be utilised in both asthma and non-asthma related respiratory distress in the child, including, but not limited to, bronchiolitis, pneumonia, croup, foreign body aspiration. This study sought to evaluate its predictive value in terms of decompensation from arrival in the ED.

The study setting was the paediatric ED of the Aga Khan University Hospital (AKUH) Karachi, a large urban tertiary care hospital, receiving patients from all over the country. The ED at AKUH is a 62-bed facility, catering to around 170 children daily and more than 60,000 patients annually. Patients are provided with initial management at the paediatric ED, after which those who have recovered are discharged. Those requiring further observation and treatment are admitted to the paediatric wards.

The primary outcome was admission to the paediatric critical care areas of our hospital, the Special Care Unit (SCU) or the Paediatric Intensive Care Unit (PICU) for support (for examples inotropic, positive pressure airway support, central vascular access and ventilation).

Inclusion criteria were ages between 1 month and 16 years of age, presenting to the AKUH paediatric ED with respiratory distress.

In order to avoid false positive screens in children with known congenital heart disease, inborn errors of metabolism and immunodeficiency were excluded as were those born prematurely at < 37 weeks' gestation.

Study procedure / protocol: Patients with respiratory distress presenting to the paediatric ED at AKUH were enrolled in the study after obtaining informed consent. At the time of initial presentation, demographic information as well as immunization status was recorded on Case Report Forms (CRF) by pre-trained research assistants. Severity of illness was assessed clinically at the initial presentation and the CRS score was obtained (CRS1), on all children before intervention.

The initial presumptive diagnosis causative for the respiratory distress, such as bronchiolitis, pneumonia, asthma, and so on, were recorded and standard management unbiased by CRS score was given to all children. A

second CRS (CRS2) was obtained 2 h after initiation of clinical management in ED.

Sample size was based on surveillance showing 7% prevalence of respiratory distress in our ED and a minimum sample size of 100 children with respiratory distress was calculated at α=5% and power of 0.8 to discriminate be- tween children admitted to ICU and those not admitted using a dichotomized score (high or moderate vs low)

The CRS was analysed as a continuous variable (0–12) and also divided into 2 categories: mild (0–3) and moderate-severe (4–12). Both the CRS scores, CRS1 and CRS2, were analysed, as well as CRSΔ, the change in CRS Frequency and percentages were calculated for categorical variables including clinical disposition, mortality and ICU admission. Means and standard deviations were calculated for continuous variables. At a univariate level, a comparison was made between the groups (mild and moderate-severe) and the baseline demographics (such as age, gender) and clinical outcomes at disposition.

Association between the CRS scores and the outcomes (ICU admission and mortality) were explored. Sensitivities and specificities were derived along with positive and negative predictive values (PPV and NPV) and likelihood ratio for positive and negative results at each score and an ROC curve for the range of scores.

Chapter 10

Reflections on study findings and public health implications

Studies 1 and 2

Randomised trial of amoxicillin for pneumonia in children in Pakistan: RETAPP

Jehan F, Nasir I, , Kerai S, Brown N, Ambler G, Zaidi AKM. Should fast breathing pneumonia cases be treated with antibiotics? The scientific rationale for revisiting management in Low and Middle Income countries. Int J Infect Dis. 2019 Aug;85:64-66. doi: 10.1016/j.ijid.2019.05.035

Jehan F, Nisar MI, Kerai S, Brown N, Balouch B, Hyder Z, et al. A double blind community-based randomized trial of amoxicillin versus placebo for fast breathing pneumonia in children aged 2-59 months in Karachi, Pakistan (RETAPP). BMC infectious diseases. 2016;16(1):1

Our study, the RETAPP trial (Jehan, Nisar et al 2019, Brown, Rizvi Kerai et al 2020) in which 4,002 children were randomized (1,999 placebo, 2,003 amoxycillin) did not show non-inferiority of placebo in terms of treatment failure (TF) relative to amoxicillin. The rates of TF were low (4.9% and 2.6%) but were of statistical significance. Mortality was extremely low with 1 death in each group. The findings are similar to, but of smaller effect than those made by Ginsburg in a similar study with the same non-inferiority margin of 1.5 in urban Malawi (Ginsburg A, Mvalo T 2018). In the latter study TF rates were 4% and 7% respectively. There were no deaths, but, because the difference exceeded the a priori stopping rule limits (O'Brien- Fleming and Pocock) at interim analysis, the trial was terminated prematurely after 1,126 children (rather than the estimated 2,000) had been enrolled.

The simple inference would be that the existing WHO recommendations are appropriate, but there are a number of caveats and avenues for further exploration

The first of these is the number needed to treat. The NNT was 44: in other words, 44 children with fast breathing without chest indrawing needed to be treated with amoxicillin to prevent one treatment failure event. This is a high

number with inherent implications for cost and antibiotic resistance. In an urban area with ready access to follow up, one could argue a case for close surveillance, particularly in the lower risk subgroups which constituted the majority in RETAPP. WHO guidance, however, needs to be generic. There is already separate guidance for high HIV prevalence areas and further subdivision by population density or proximity of home to health centre, might be confusing and counterproductive. Nonetheless, this debate needs to be continued.

The second, related issue is of targeting treatment to higher risk groups. We found fever and wheeze in particular to be stronger predictors of TF. In children with fever (a temperature of > 37.5C at initial presentation) the rates of TF were 7.9% and 3.9% (difference/ 95% CI 4.1%, 1.5% to 6.7%) in the placebo and amoxicillin groups respectively. In the afebrile children the proportions with TF were much closer and of only borderline significance at 3.5% vs 2.1%, a difference of 1.4% (95% CI 0.2% to 2.7%). Similarly, in children with wheeze the proportions were 10.1% and 3.1 (difference 7.0 (CI 1.4 to 12.7%) while in those without 4.5% vs 2.6% (1.9% difference, CI 0.7 to 3.1%). Children with fever and wheeze were less than half the total and, though the trial was not powered to examine these subgroups, selective treatment is a question with real economic and epidemiological implications that requires exploration.

The third issue relates to likely changes as vaccine uptake improves given that only 50% of the participants had received full recommended immunisations by age. The trial provides a snapshot of the current difference between amoxicillin and placebo, but as coverage of conjugate vaccinations improves so might the differences between TF rates. Time will tell, but we should not exclude a further similar study in the future when coverage is near universal

A final issue relates to duration of antibiotic treatment in relation to a recent trial by Ginsburg and colleagues in Malawi testing a 3 vs 5 day course of amoxicillin in fast breathing pneumonia with chest indrawing (Ginsburg, Mvalo et al 2020). They found no evidence of inferiority of the shorter course, but, as Chang's commentary (on both this study and RETAPP) cautioned, the non-inferiority margin of 1.5 might have been too wide to detect subtle but important differences (Chang and Grimwood 2020).

The next chapters of this intriguing story will be pivotal.

Recurrent fast breathing pneumonia: The role of home environment.

Brown N, Rizvi A, Kerai S, et al. Recurrence of WHO-defined fast breathing pneumonia among infants,its occurrence and predictors in Pakistan: a nested case–control analysis. BMJ Open 2020;10:e035277. doi:10.1136/

The starting premise of this paper, an observational study nested within the RETAPP trial, was an exploration of the role of potentially modifiable individual and environmental factors with a focus on indoor air pollution (IAP) in predicting recurrence of fast breathing pneumonia. This phenotype represents a vulnerable child with little capacity to recover from recurrent stressors. To remove the potential confounding effect of age on vaccination incompleteness and pneumonia incidence (both higher in infants) we matched by age group. With the rider that the sample might have been underpowered to show subtle differences by exposures, there were no statistically significant associations between individual characteristics, markers of IAP or poor sanitation and recurrence of fast breathing pneumonia. However, household type, temporary, adobe katcha dwelling significantly predicted recurrence. As argued in the discussion, housing type is a marker of poverty and probably (though not specifically explored) of transient residence, children of migratory families vulnerable in a range of tangible and intangible ways.

Indoor air pollution is a complex area, particulate matter alone being derived from a wide range of sources – burning dung, crop residues, wood and charcoal, spores and pollen. In a systematic review of the effects of IAP on respiratory health, Adaji found no effect of carbon monoxide alone, but a consistent adverse effect of particulate matter of PM2.5 when measured by solid fuel use though not when directly measured (Adaji, Ekezie et al 2019).

Two randomized trials (Malawi and Guatemala) of improved, lower biomass dense interventions (fuel and Plancha stoves) showed little effect on primary pneumonia outcome except in severe pneumonia in the Guatemala trial but some effect on reducing exposure concentration (Mortimer, Ndamala et al 2017 and Smith, McCracken et al 2011).

In Mexican women, Romieu, however, despite poor adherence found the Patsari stove reduced respiratory symptoms (rate ratio [0•29 [95% CI 0•11–0•77] for wheeze) and lung function decline (31 mL vs 62 mL over 1 year; p=0•01) in those who used the stove. (Romieu, Riojas-Rodríguez et al 2009).

The two paediatric trials have findings analogous to our own, particulate matter only being part of a complex whole environment exposure. This does not mean, of course, that efforts to incorporate access to cleaner fuel and better stoves should cease. On the contrary, they will be key components in the overall strategy but cannot alone solve the problem. Our findings suggest that the ‘package’ of exposure inherent to poverty increases risk and this is likely to

include nutritional, immunological, educational, literacy-related, family size (family planning and adolescent health) factors over the life course.

A discussion of economic interventions is beyond the scope of this thesis, but, the consistency of the association between poverty and pneumonia reinforces the view that any single vertical programme alone is unlikely to succeed.

Efficacy of zinc as adjunctive treatment for pneumonia in children in Low and Middle Income Countries: a systematic review and meta-analysis

Nick Brown, Antti Kukka, Andreas Mårtensson. Efficacy of zinc as adjunctive treatment for pneumonia in children in Low and Middle Income Countries: a systematic review and meta-analysis. BMJ Paediatrics Open 2020;4:e000662. doi:10.1136/. bmjpo-2020-000662A

Our meta-analysis study for which 11 RCTs met the a priori criteria showed no evidence of benefit of adjunctive zinc in either reducing proportional treatment failure or mortality rate. The findings were robust to sensitivity analysis by high risk of bias studies. There were effects in a few studies in recovery times in certain subgroups (for example by adequate zinc status and under-nutrition), but, these were inconsistent and the pooled result (HR 1.01) strongly suggested a Null effect.

The hypothetical benefits of zinc are attractive given its known immune enhancing properties, reduction of all-cause mortality when given prophylactically at population level and the unequivocal benefits in reducing time to recovery from gastroenteritis, a use which the WHO endorses.

The last meta-analysis in this area using studies published up to 2015 (Wang 2018) showed a reduction in mortality, but was heavily weighted by a trial with a high risk of outcome bias (Srinavasan, Ndeezi et al 2012). Three earlier meta-analyses (2011, 2012 and 2016) like ours showed no effect.

More than 50% of the children in the trials our analysis had severe pneumonia and one could argue the case for adequately powered trials in children with (the much commoner) non-severe/fast breathing phenotype. However, these children have very high rates of spontaneous recovery (see RETAPP and Malawi studies) so any extra benefit is likely to be marginal.

In short, like Vitamin A in the past (Brown, Roberts 2014), there is no evidence for the adjunctive use of zinc in pneumonia in children in Low and Middle Income Countries.

In conclusion, there is a case to be made for better investment of resources for improvement of the identification of the child with pneumonia with signs of severe disease, of early recognition and treatment of hypoxia and of rapid referral for secondary management rather than further research into an

adjunctive treatment with at best marginal treatment in inconsistent subgroup phenotypes.

The clinical respiratory score predicts paediatric critical care disposition in children with respiratory distress presenting to the emergency department.

Kanwal Nayani, Rubaba Naeem, Owais Munir, Naureen Naseer, Asher Feroze, Nick Brown, Asad I. Mian. The clinical respiratory score predicts paediatric critical care disposition in children with respiratory distress presenting to the emergency department. BMC Pediatrics (2018) 18:339. https://doi.org/10.1186/s12887-018-1317-2

Our study assessed a tool, the clinical risk score (CRS), validated in a high income setting, but not previously examined in an LMIC. It fulfils the prerequisites for a screening tool (speed of administration, low cost and the use of only readily available physiological parameters). It was found to have high sensitivity (94% (95% CI 79.8% to 99.3%)) and negative predictive value (94% (82% to 98%)) for later intensive care requirement in the setting of a tertiary paediatric emergency department in Pakistan. Like most such tools, the low false negative rate was balanced by a moderately high false positive rate (specificity 40% (95% CI 35 % to 45%)), so, though few sick children were missed, a number received unnecessarily escalated care.

Though this might seem a reasonable trade off and the temptation is to unequivocally endorse the tool, there are reasons to be cautious in terms of the design. Firstly, there was no direct comparison with other tools. Secondly the observations were not fully blinded to admission CRS. Thirdly, the study was observational rather than (randomized controlled) interventional with all the potential biases and confounding to which these are susceptible.

Paediatric early warning (PEWS) scores using either triggers or composite thresholds have proliferated over the last few years despite weak evidence of efficacy. The large (21 hospitals in 7 countries (Belgium, Canada, England, Ireland, Italy, New Zealand, and the Netherlands) and 144,000 children) EPOCH cluster RCT in the US (Parshuram, Dryden-Palmer et al 2018) showed no evidence of a reduction in mortality in children assessed with the (widely used) bedside PEWS in addition to standard care against standard care alone though a marginal effect on predicting deterioration. Whether other measures of physiological compromise such as lactate, pH, pCO2 will augment the predictive value of the largely clinical scores remains to be seen.

There is now an appreciation that the tools are, to some extent, context dependent a reflect the clinical environment (and human error) in which they are used (Chapman and Peters 2019). The time feels right to focus on modifying settings, enhancing access to and tightening procedural infrastructure within institutions.

Dedication

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