FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

NEONATAL HOSPITAL MORTALITY in SOUTH VIETNAM

Alexandra Yasmin Kruse

The International Child Health Research Unit
The Department of Paediatrics and Adolescent Medicine
Rigshospitalet – Copenhagen University Hospital, Denmark

PhD thesis 2013

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MD, Paediatrician

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The International Child Health Research Unit
The Department of Paediatrics and Adolescent Medicine
Rigshospitalet – Copenhagen University Hospital
Denmark

Supervisors

Professor Freddy Karup Pedersen
The International Child Health Research Unit
Department of Paediatrics and Adolescent Medicine
Rigshospitalet – Copenhagen University Hospital, Denmark

Professor Gorm Greisen
Department of Neonatology
Rigshospitalet – Copenhagen University Hospital, Denmark

PhD Lone Graff Stensballe
Department of Paediatrics and Adolescent Medicine
Rigshospitalet – Copenhagen University Hospital, Denmark

Appraisal Committee

Professor Ib Christian Bygbjerg
Department of International Health, Immunology and Microbiology
University of Copenhagen, Denmark

Professor Lars Åke Persson,
International Maternal and Child Health
University Hospital of Uppsala, Sweden

PhD Bo Mølholm Hansen
Department of Neonatology
Rigshospitalet – Copenhagen University Hospital, Denmark

Public Defense

April 19th 2013, Medial Museion, Bredgade 62, Copenhagen

Cover page

Dr Chuong and orphan at PH1 Neonatal Intensive Care Unit after Tet (Chinese New Year)

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1. PREFACE

This thesis is based on the following papers:

I AY Kruse, BT Ho, CN Phuong, LG Stensballe, G Greisen and FK Pedersen. *Prematurity, Asphyxia and Congenital Malformations Underrepresented among Neonates in a Tertiary Paediatric Hospital in Vietnam*, BMC Pediatr 2012, 12: 199

II AY Kruse, B Ho, CN Phuong, H Ravn, LG Stensballe, G Greisen and FK Pedersen. *Predictors of Neonatal Death in a Paediatric Hospital in Vietnam*, submitted.

III AY Kruse, DHT Chuong, CN Phuong, TD Duc, LG Stensballe, J Prag, JAL Kurtzhals, G Greisen and FK Pedersen. *Neonatal Blood Stream Infections in a Paediatric Hospital in Vietnam: a Cohort Study*, submitted.

IV AY Kruse, CN Phuong, B Ho, LG Stensballe, FK. Pedersen and Gorm Greisen. *Prospective Audit Study of Neonatal deaths in a Paediatric Hospital in Vietnam*, to be submitted.

This thesis builds on 30 years of development cooperation between Paediatric Hospital no 1 and Danish paediatricians facilitated by The Danish Vietnamese Association. In the recognition of the need to explore neonatal mortality to enable further reduction in Vietnamese child mortality, these studies were planned. The thesis is part of a research capacity building project.

The culture, perception and priorities differ between the Danish and Vietnamese society. This difference was part of the working conditions during this research work. Other conditions were the Danida sponsorship, the guest-host relation, and the sensitive nature of the topic. Neonatal mortality is one of the key indicators to measure and compare countries´ health and development level. Further, transparency in public statistics and management is tightly controlled in Vietnam. These conditions should be recognized as part of the framework, in which the studies were carried out.

In spite of continued effort, it was difficult to achieve a satisfying understanding of the context in which PH1 operates and how the families of ill neonates navigate in the health care system. The dialogue with other stakeholders could have been more fruitful, including access to statistics, guidelines and agreements. PH1 somewhat remained an “island in an unknown sea”. Hopefully other studies will uncover this issue.

2. ACKNOWLEDGEMENTS

The thesis is based on studies carried out in Paediatric Hospital number 1 in Ho Chi Minh City in Vietnam in the years 2009-2012.

The PhD study was sponsored by Danida, The Danish International Development Agency, The Ministry of Foreign Affairs of Denmark. The studies were also supported by grants from The Faculty of Health and Medical Science at Copenhagen University, The Capital Region of Denmark, King Christian the Xth Fund, Dagmar Marshall Fund and Torben Iversen's Travel Fund

I am grateful to the families and staff of the Paediatric Hospital No 1, who made the studies possible. Particularly, I wish to thank *Cam Ngo Phuong*, *Binh Ho* and *Do Huu Thieu Chuong* for your trust and openness to include me in your work, for your generosity and guidance.

I am much indebted to my supervisors *Freddy Karup Pedersen*, *Gorm Greisen* and *Lone Graff Stensballe*, Rigshospitalet, each of whom contributed in so many different ways. Thanks for sharing your scientific insight and reflexion, for inspiration, for engagement in discussions and for constructive suggestions. Thank you for the support, encouragement and concern during a sometimes bumpy road.

Thanks to *Henrik Ravn*, Statens Serum Institut for statistical guidance and to *Jørgen Kurtzhals*, Rigshospitalet, for essential microbiological contributions.

I value the cooperation with *Dinh Phuong Hoa*, Reproductive Health, Ministry of Health, Vietnam and the Danish Vietnamese Association, especially *Jørgen Prag*. Also thanks to *Laura Merson*, Oxford Clinical Research Unit – Vietnam, for both enthusiastic support and critical questioning.

I would like to express my thanks to *Lina Steinrud* for the methodological ping-pong and stimulating discussions and to my other fellow research colleagues at The Research Unit of Women's and Children's Health at Rigshospitalet for good company.

Thanks to my dear friend and colleague *Liselotte Gluud* for competent input and support.

Thanks to my husband *Christian* and our boys *August* and *Julius*, who settled with me in Ho Chi Minh City during this work. I dearly appreciate your curiosity, joy of adventure, support and patience on this journey.

3. SUMMARY

3.1 Summary

Of the 4 million neonates (≤ 28 days of age) dying annually, the vast majority die in developing countries. Most die of infections, prematurity, asphyxia and congenital malformations. Compared to the decrease in child mortality, achievements to reduce neonatal mortality lag behind, globally and in Vietnam. An estimated 17,000 neonates die annually in Vietnam. Considering that 90% of women deliver in health care facilities, the majority of neonates presumably die in hospital settings. Current knowledge about neonatal morbidity and mortality, however, is limited.

We explored neonatal mortality in the tertiary Paediatric Hospital number 1 in Ho Chi Minh City, Vietnam (PH1). In a 12 month period in 2009 – 2010, 5,763 neonates were admitted. The case fatality rate was 4%. Another 1% was discharged alive after withdrawal-of-life-sustaining-treatment.

In our first study, we described the neonatal hospital population in PH1 and compared to the neonatal population of Rigshospitalet, Copenhagen, Denmark. Our findings indicate that prematurity, asphyxia and congenital malformations were significantly underrepresented in the hospital, compared to both Rigshospitalet and to the catchment population of the hospital. Further, almost a quarter of the neonates had mild conditions, which could probably have been treated sufficiently at lower levels. The findings suggest that utilization of the specialized care available in PH1 may not be optimal.

In our second study, we examined pre-hospital predictors of death in the hospital among a vulnerable sub-group of 2,196 neonates with a case fatality rate of 9%. The predictors were socio-demography, pregnancy-delivery, neonatal history and clinical status at admission. Notably, ethnicity, parental education and gender were not associated with death, once admitted to the hospital. Impaired respiration, circulation and consciousness at admission were associated with an increased risk of death, which underlines the importance of vital signs at admission.

In our third study, we investigated the 385 neonates, who had blood stream infections defined as positive blood cultures. Most infections were late onset. Frequent isolates were *Klebsiella* spp., *Acinetobacter* spp. and *Escherichia* coli. No *Streptococcus* group B was identified. The septicaemia related case fatality rate in the study population was 16% and Gram-negative infections carried the highest mortality. Antibiotic resistance was common. Surveillance of neonatal blood stream infections in the hospital is recommended.

In our fourth study, we investigated death cause and potentially avoidable in-hospital risk factors of death (235 neonates) and expected death (67 neonates discharged alive after withdrawal-of-life-sustaining-treatment). Major causes were congenital malformations, infections, prematurity and asphyxia. Among the 85% of the 71 cases with a relatively good prognosis at arrival to the hospital, we identified 6 risk factors, which could be addressed without implementation of new technologies or major organizational changes. The risk factors were related to management of general danger signs, septicaemia, internal transfer, equipment, and parental misperception of prognosis.

In conclusion, our studies increase the understanding of neonatal hospital mortality in Vietnam. To decrease neonatal mortality in the study hospital and possibly in similar hospitals, we suggest: increased access to specialized care for vulnerable groups of neonates, further research on early warning scores, implementation of blood stream infection surveillance, and addressing the potentially avoidable risk factors identified in the hospital. Furthermore, implementation of standard mortality audit could be considered.

3.2 Danish summary

Blandt de 4 millioner spædbørn (≤ 28dage) der dør årligt, dør langt størstedelen i udviklingslande. De fleste dør af infektioner, præmaturitet, asfyxi og kongenitte malformationer. Sammenlignet med reduktionen i børnedødelighed, halter reduktionen i spædbarnsdødelighed efter, globalt og i Vietnam. Estimeret 17,000 spædbørn årligt i Vietnam. Halvfems procent af kvinderne føder på hospital og følgelig formodes størstedelen af spædbørnene at dø i hospitalsregi. Vores nuværende viden om neonatal morbiditet og mortalitet er imidlertid begrænset.

Vi undersøgte neonatal mortalitet på det tertiære Børnehospital nummer 1 i Ho Chi Minh City, Vietnam (PH1). I en 12 måneders periode i 2009-2010 blev 5,763 spædbørn indlagt. Case fatality rate var 4%, yderligere 1% blev udskrevet i live efter indstilling af livsbevarende behandling.

I vores første studie beskrev vi den neonatale hospitalspopulation på PH1 og Rigshospitalet, København, Danmark. Vores fund indikerer, at præmaturitet, asfyxi og kongenitte malformationer var signifikant underrepræsenteret på hospitalet, sammenlignet med både Rigshospitalet og med hospitalets baggrundspopulation. Desuden havde næste en fjerdedel af spædbørnene milde sygdomme, som formentligt kunne være blevet behandlet sufficient på et lavere niveau i sundhedssystemet. Disse fund indikerer, at den specialiserede behandling som PH1 råder over, måske ikke udnyttes optimalt.

I vores andet studie undersøgte vi præ-hospitals prædiktorer for død på hospitalet blandt en sårbar subgruppe på 2.196 spædbørn med en case fatality rate på 9%. Prædiktorene var socio-demografi gravidtet-fødsel, neonatal-anamnese og klinisk-indlæggelses-status. Bemærkelsesværdigt var etnicitet, forældre uddannelse og køn ikke associeret til død, efter indlæggelse på hospitalet. Påvirket respiration, cirkulation og bevidsthed ved indlæggelsen var associeret til øget risiko for død. Det understreger vigtigheden af vitale værdier ved indlæggelsen.

I vores tredje studie undersøgte vi 385 spædbørn med blood stream infections defineret som positiv bloddyrkning. De fleste af infektionerne var late-onset. De hyppigste isolater var *Klebsiella* spp., *Acinetobacter* spp. og *Escherichia* coli. Vi fandt ingen *Streptococcus* group B. Den sepsisrelaterede case fatality rate i studiepopulationen var 16% og spædbørn med Gram-negative infektioner havde den største risiko for at dø. Antibiotika resistens var udbredt. Det anbefales at neonatale blood stream infections overvåges på hospitalet.

I vores fjerde studie undersøgte vi potentielt undgåelige risikofaktorer for død (235 spædbørn) og forventet død (67 spædbørn udskrevet i live efter indstilling af livs-bevarende behandling). De hyppigste årsager var kongenitte malformationer, infektioner, præmaturitet og asfyxi. Blandt 85% af 71 cases med relativ god prognose ved indlæggelse identificerede vi 6 risikofaktorer, som ville kunne adresseres uden implementering af ny teknologi eller større organisationsforandringer. Risikofaktorerne var relateret til håndtering af generelle faresymptomer, sepsis, interne overflytninger, udstyr og fejlvurdering af prognose.

Samlet konkluderer vi, at studierne øger forståelsen af neonatal hospitalsmortalitet i Vietnam. For at reducere denne, på studiehospitalet og muligvis på andre lignende hospitaler, foreslår vi: at øge adgangen til specialbehandling for sårbare grupper af spædbørn, yderligere studier af early warming scores, implementering af overvågning af blood stream infections og adressering af de potentielt undgåelige risikofaktorer identificeret på hospitalet. Desuden kunne det overvejes at indføre mortalitetsaudit.

4. ABBREVIATIONS

BSI	Blood stream infections
CI	95% Confidence Intervals
ER	Emergency room
ICD10	The International Classification of Diseases, 10th revision
MDG	Millennium Development Goals
NMR	Neonatal Mortality Rate (number of deaths ≤ 28 days of age /1000 live birth)
NNT	Number Needed to Treat
NICU	Neonatal Intensive Care Unit
OR	Odds Ratios
PH1	Paediatric Hospital number 1
RH	Department of Neonatology, Rigshospitalet, Copenhagen, Denmark
SICU	Semi Intensive Care Unit
VP	Very premature (gestational age <32 weeks)
VLBW	Very low birth weight (birth weight ≤ 1500g)
WLST	Withdrawal-of-life-sustaining-treatment

5. INTRODUCTION

More than 4 million infants die annually within the first month of life, the vast majority in developing countries. Most still die unnamed and unrecorded at home accounting for more than 40% of the children dying (under 5 years of age). The proportion is growing as achievements for neonates (≤ 28 days of age) lag behind their older peers (1;2). Until the 1990s there was a common fatalistic perception and neonatal mortality caught little attention by both researchers and policymakers. In 2000 neonatal mortality entered the global health agenda with the launch of The Millennium Development Goals (MDG) and the integrated approach of continuum of care for women and children including neonates. Addressing neonatal survival is critical to achieving MDG for child mortality reduction (3-7).

6. BACKGROUND

6.1 Global mortality

As 98% of the deliveries in the world occur in countries with incomplete vital registration, figures of global neonatal mortality rely on estimates and data modelling. Globally, the major causes of neonatal mortality are infection (36%), prematurity /low birth weight (28%), asphyxia (23%) and congenital malformation (7%). These conditions also cause significant morbidity and long term developmental deficit in survivors. The global Neonatal Mortality Rate (NMR) is 23/1,000 live births, with the highest rates in Sub-Saharan Africa and the highest numbers in South Central Asia (1;2;8). Reported NMR in Vietnam is 12/1,000 live births compared to 2-4/1,000 live births in Europe and up to 50/1,000 live births in Sub Saharan Africa {2012 25 /id}. The first days are the most vulnerable time of the neonatal period (1).

6.1.1 Prematurity

Globally, 1 in 10 is born premature (<37 gestational weeks). Prematurity and its complications is an underlying cause in half of neonatal deaths. As gestational age is often unknown, birth weight is used a proxy. Very prematurity (VP<32 gestational weeks) and very low birth weight (VLBW ≤1500 g) have a particular high mortality risk and represent approximately one quarter of premature neonates. The global range of estimated regional incidence rates of prematurity is 90-140/1000 live births. For Asia the range is similar (10-14). For rough comparison, we assumed the incidence to be steady over regions. There are differences, however, e.g. reliability of data and provider-induced delivery differ.

6.1.2 Infections

Neonates are particularly susceptible to infections (15;16). Lethal infections include septicaemia, meningitis, pneumonia, diarrhoea and tetanus.

6.1.3 Asphyxia

The definition of the clinical syndrome of birth asphyxia has been disputed. It is defined by WHO as a neonate who fails to initiate and maintain regular breathing. Whereas others include specific clinical and para-clinical findings (Agar score and umbilical cord pH), which are often not accessible in resource-limited settings (17-19). The term intrapartum-relation is now more often used and exclude other causes such as major malformations and prematurity. The diagnosis is sensitive, as it may indicate suboptimal delivery care, including insufficient fetal monitoring and neonatal resuscitation (20) The incidence rate is estimated to 2-26/1000 live births, depending on NMR (21). For Vietnam this corresponds to a rate of 7/1000 live births.

6.1.4 Congenital malformations

Major congenital malformations are included in the global death cause estimates. They include structural defects which are lethal or carry a high mortality. There is no specified definition of the term or which malformations are included (22), e.g. some include inborn errors of metabolism and chromosomal anomalies (23). The rough estimates

of crude incidence rates of the different congenital malformations may be considered steady over regions. However, some variations are expected, since genetic and environmental causes may vary and termination of pregnancy following prenatal diagnosis also varies (23). In our study (*paper I*), we included oesophageal atresia, gastroschisis, omphalocoele, diaphragmatic hernia and congenital heart diseases (23-33).

6.2 Vietnam

Vietnam was a low income country at the time of the study, but has now risen to a lower middle income country (34). As a socialist country it has prioritized education and health care and focused more on the group and society than on the individual. It has a 2-children policy and a cultural male preference, which may explain the rising sex ratio imbalance at birth (35;36). No valid vital registration system is in place and health indicator figures rely on Multiple Indicator Cluster Surveys and Demographic and Health Surveys.

6.2.1 Health care in Vietnam

In Vietnam health care is free for children less than 6 years of age. It means outpatient treatment is based on user-fees, while hospitalization is free of charge. However, for hospitals to have their expenses reimbursed, the child has to be legally entitled to health care. Hence the child has to be Vietnamese citizen, adhere to the referral system unless an emergency, and the treatments have to be included in a specified positive-list. In practice, official fees can be imposed on the family. Additionally, unofficial incentives are common (37;38). Further, transport and indirect expenses such as lost income and food during the hospital stay is a concern for families. The private health care sector is growing and based on user-fees.

6.2.2 Neonatal mortality and morbidity in Vietnam

In Vietnam estimated 17,000 neonates die annually (39), but neonatal mortality may be under-reported (40-43). It is the responsibility of the family to have birth and death certificates issued. If a neonate dies, the family may not prioritize the legal paper work. The family is grieving, may not understand the purpose of certificates, or foresee future problems to comply with the 2 children-policy.

Vietnam has achieved substantial reductions in child mortality (44), but to a lesser extent for neonates (45). Since institutional deliveries account for almost 90% of deliveries (44;46;47) and the majority presumably remains hospitalized in the first vulnerable days after delivery, the majority of neonatal deaths are likely to occur in hospital settings. However, great regional disparities exist (47;48) and a community study in a rural province in North Vietnam, found a quarter of neonatal deaths occurring outside the health care system (49).

To our knowledge there is a paucity of data and peer-reviewed studies available on neonatal hospital morbidity and mortality.

6.2.3 Paediatric Hospital No 1

The tertiary hospital Paediatric Hospital Number 1 (PH1) in Ho Chi Minh City is the referral hospital for the 32 southern provinces with an estimated population of 32 million. The hospital has 1,200 beds covering 17 sub specialties, including neonatology and surgery. It has 1.2 million outpatient visits and 86,000 admissions annually. Approximately 1/3 of the patients admitted live in Ho Chi Minh City and 2/3 live in the southern provinces. The vast majority, approximately 95%, are referred from other health care facilities. The neonatal department includes basic, semi-intensive and intensive care units with a total of 150 beds. The bed occupancy during the study period was 154%. PH1 is responsible for organizing neonatal care in the South and offered the most specialized neonatal care in the country including exchange transfusion, surfactant replacement, ventilator support and surgery.

In the hospital, withdrawal-of-life-sustaining-treatment (WLST) was practised, when the staff

or family perceived the prognosis too poor. The infant would die in hospital or be discharged alive to die at home. End of life decisions is a well described dilemma in care of infants, implying difficult ethical considerations (50-56).

In 2009, the potential catchment population comprised of 726,578 live births in South Vietnam corresponding to approximately half of the deliveries in the country (57). The sex ratio at birth was 109.7 boys/100 girls (58).

PH1 context
Specialized neonatal care in the South was provided by 4 tertiary hospitals situated in Ho Chi Minh City: 2 paediatric hospitals (including PH1) and 2 maternity hospitals. In 2009, the other tertiary paediatric hospital admitted 3,252 neonates (11% birth weight < 2,500 g) and had no neonatal intensive care unit. The 2 maternity hospitals performed 67,655 deliveries (more than 95% of the deliveries registered in the city). Of these, 18,328 (28%) were reported to be admitted to the neonatal units, including the neonatal intensive care units. No neonatal surgery was offered in the maternity hospitals.

6.3 Comparison to Denmark

We compared the hospitalization rates of selected conditions in PH1 to those at The Department of Neonatology, Rigshospitalet, Copenhagen, Denmark (RH). The hospital serves as the local hospital to a part of Copenhagen and as the tertiary general hospital to East Denmark. Obstetric care includes centralization of deliveries with a gestational age <28 weeks. The neonatal department included intensive care and 36 beds. Of the referring hospitals, 6 provide specialized care; one had limited ventilator capacity and none offered neonatal surgery. In addition to the therapies offered at PH1, RH provided inhaled nitric oxide, controlled hypothermia, extracorporeal membrane oxygenation and extensive surgical procedures. In 2009, RH case fatality rate was 5% (52/1129). The catchment population was 29,161 live births corresponding to 1/25 of the PH1 catchment population. The birth sex ratio was 105 (male/100 female) (59).

6.4 Predictors and clinical risk scores

Clinical risk scores have been developed to predict hospital mortality among neonates (60;61) and among children (61-63) in developed countries. In developing countries, risk scores have mainly focused on guiding referral of young infants to hospital-level care (61;64;65). Scores predicting neonatal mortality risk at the time of hospital admission has had less attention. This would be particularly relevant in countries like Vietnam, where the majority of deaths presumably occur in hospitals.

6.5 Blood stream infections

Septicaemia is defined as positive blood culture (blood stream infections, BSI) and systemic clinical signs (16;66-68). In the absence of consensus of specified diagnostic criteria, blood culture is considered the gold standard to establish the diagnosis (68). Several predictors of septicaemia have been investigated (69-74), but septicaemia remains difficult to diagnose at presentation and prompt empirical treatment is prescribed. Later antibiotics are adjusted according to blood culture and clinical response. The aetiology of BSI varies considerably. Compared to high-income countries, neonatal septicaemia in lower-income countries is more frequent, more commonly caused by Gram-negative bacteria and mortality higher. Furthermore, antibiotic resistance is an increasing problem (15;16;75-79).

6.6 Audit

Clinical audit is an established part of quality improvement within the health care system, especially in obstetrics (80-83). The complete audit cycle consists of several steps: establishing best practice criteria, observing current practice, feedback of findings and setting local standards, implementing changes, and evaluation of outcomes. The hospital mortality audit is a structured evaluation of death cause and

potentially avoidable risk factors in relation to health care performance. A constructive no-shame, no-blame atmosphere is crucial to motivate staff and achieve improvements (84-87). The audit impact on mortality reduction has been disputed, especially in lower income countries. A possible benefit probably relies on baseline performance and feedback (88-92).

7. HYPOTHESIS AND AIMS

The hypotheses were:

Paper I

The neonatal population (admission age ≤ 28 days) at PH1 has not been studied systematically previously. We assumed that the selection of the neonates admitted to the hospital was based not only on medical reasons.

Paper II

Socio demography and clinical admission conditions were predictors of mortality in neonates at PH1.

Paper III

The neonatal BSI in PH1 resembled other resource-limited settings; the majority of isolates were pathogenic and widely resistant to antibiotics prescribed.

Paper IV

Causes of neonatal deaths in PH1were not clarified. Potentially avoidable risk factors in the hospital might contribute to neonatal death.

The specific aims were:

Paper I

To describe the PH1 neonatal population. Particularly to compare the hospitalization rates of prematurity, asphyxia and selected congenital malformations in PH1 to Rigshospitalet (Denmark) and to catchment population estimates.

Paper II

To identify admission predictors associated with death among vulnerable neonates in PH1. Predictors of death were socio-demography, pregnancy-delivery, neonatal history and clinical condition at admission.

Paper III

To describe the patterns of neonatal BSI at PH1 including species, onset and antibiotic susceptibility. Furthermore, to assess the septicaemia related mortality among neonates with blood stream infections.

Paper IV

To characterize neonates dying in PH1 by assigning causes of death and identifying potentially avoidable risk factors. Causes were classified according to The International Classification of Diseases 10th revision and The Child Health Epidemiology Reference Group.

8. PATIENTS AND METHODS

8.1 Design

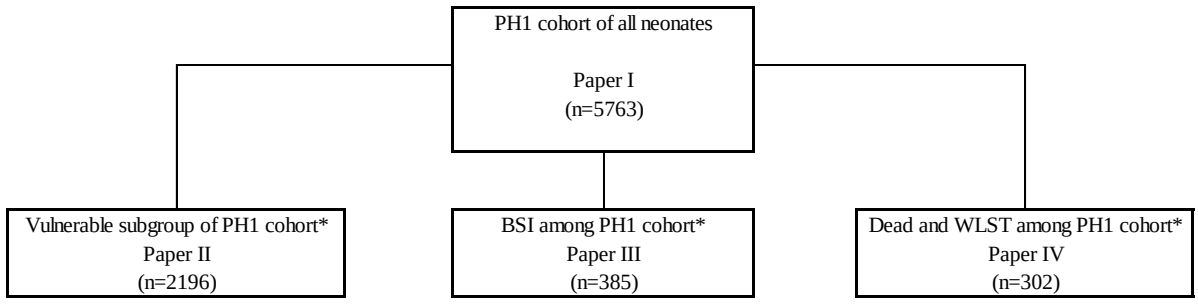
A prospective cohort of all neonates (≤ 28 days of age) admitted to PH1 consecutively in the 12 months study period February 2009 – February 2010 was established. This cohort was the study base of papers I-IV.

Paper I was a comparative study
Paper II and III were cohort studies
Paper IV was a qualitative audit study

8.2 Patients

Figure 1 shows the study populations in papers I-IV. Overall 5,802 neonates (≤ 28 days of age) were admitted during the study period. Thirty-nine neonates had incomplete data from the central hospital registry and were excluded, none died or had WLST. The remaining 5,763 neonates (>99%) were available for analysis and included in the PH1 cohort.

Figure 1
Study populations in papers I-IV



*The study populations are overlapping. PH1 (Pediatric Hospital no 1), BSI (blood stream infections), WLST (discharged alive after withdrawal-of-life-sustaining-treatment)

Twenty-two neonates were registered as dead on arrival. Four of these showed signs of life. It was not possible to change the registration of these neonates for the purpose of the present studies and hence they were not included in the PH1 cohort.

8.2.1 *Paper I*
In the comparative study the population comprised of all neonates admitted (n=5,763) to PH1. The neonatal population in RH was used for comparison. The population from RH comprised all neonates admitted during the years 2001-2010 (n=8,849). The longer study period in RH was based on the lower number of admissions.

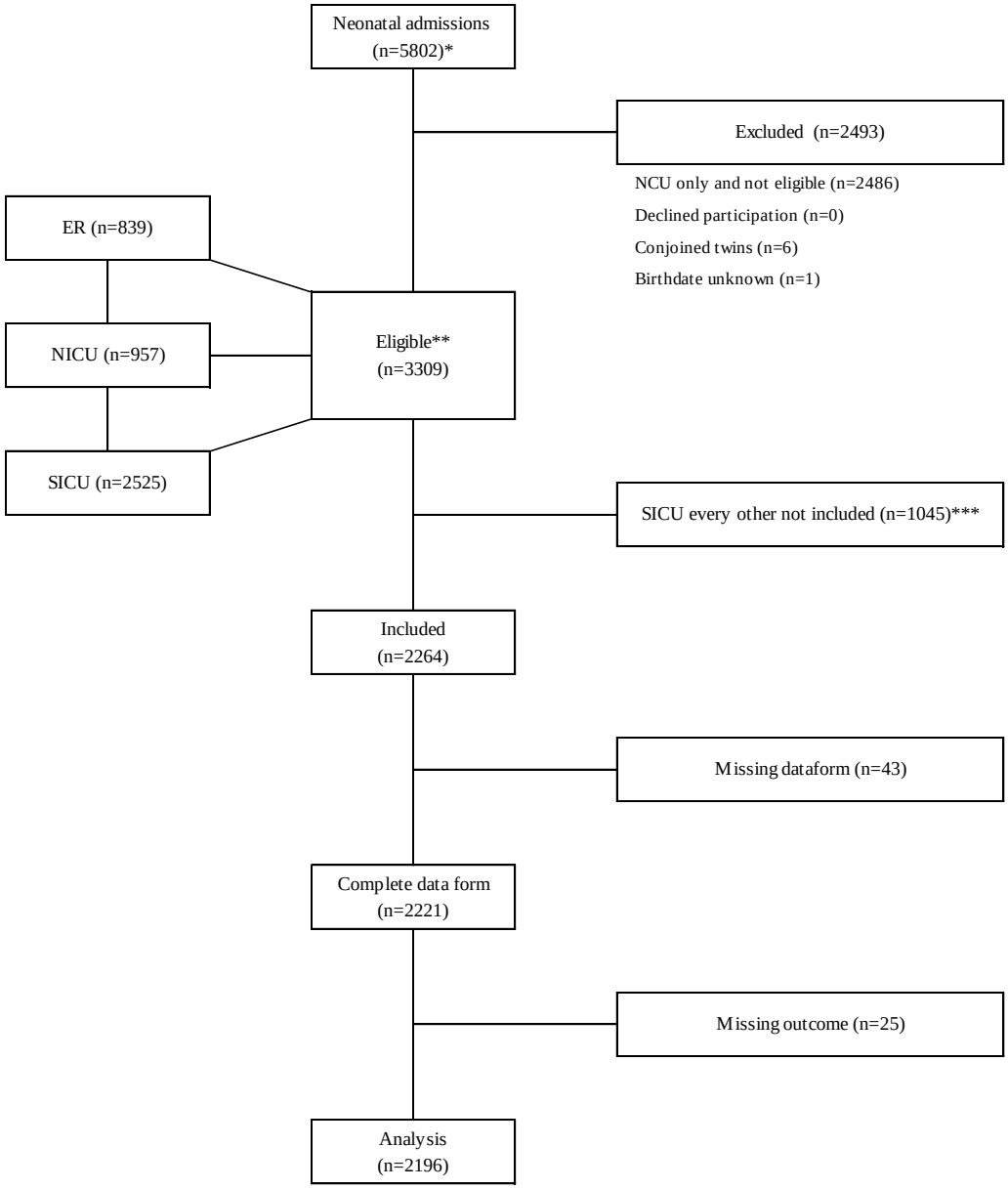
8.2.2 *Paper II*
The study population in the predictor study comprised of a sub group of the PH1 cohort (n=2,196).

Sample size
Before initiating the study, the required sample size was calculated. Assuming a mortality risk of 5% and a predictor prevalence of 12%, the inclusion of 2,151 patients would enable us to detect odds ratios (OR) of 2, at a significance level = 0.05 with a power = 0.8. Based on previous admission figures we evaluated the sample size feasible.

Patient inclusion
Neonates admitted to the following units: emergency room (ER), neonatal intensive care unit (NICU) and semi-intensive care unit (SICU) were eligible for inclusions. Neonates admitted to the basic neonatal care unit were not eligible. All eligible neonates from the ER and NICU were included consecutively. From SICU every second (1:1) eligible neonate was included by project staff from the admission book kept by the clinical nurse in charge. This selection was applied to focus on the most vulnerable neonates, to reduce workload in the department, and to maximize data completion. Patients were included only once. The inclusion criteria were: neonate, family consent, admission to the ER, NICU or SICU. Exclusion criteria were: previous inclusion, unknown birth date (foundling) and conjoined twins.

Patient flow chart
Figure 2 shows the patient flowchart. Of the total neonatal population of 5,802 neonates, 2,493 did not meet the inclusion criteria. The remaining 3,309 neonates from the 3 inclusion wards were eligible, of which 1,012 was assessed for eligibility more than once because of internal transfers. Accordingly, more than half of the neonates in SICU were included. Hence 2,264 neonates were enrolled, for which 2,221 questionnaires were completed (missing n=43). Due to missing discharge data (n=25), 2,196 neonates (38% of all neonates) were available for our final analysis. No families declined participation.

Figure 2
Patient flow chart of the PH1 sub group included in paper II



NCU (Neonatal Care Unit), ER (Emergency Room), NICU (Neonatal Intensive Care Unit), SICU (Neonatal Semi-Intensive Care Unit)
*The number is higher than in figure 1, as it also includes neonates exluded later due to missing data in the hospital registry
**Because of internal transfers, ward numbers add up to more than the total eligible number
*** Because of internal transfers , less than every half of SICU neonates were not included

8.2.3 *Paper III*
The BSI study population consisted of all neonates with confirmed BSI (n=385) in the PH1 cohort (5763). In total 399 (18%) of 2,202 blood cultures performed were positive. Fourteen patients had 2 positive cultures, with different isolates at different times (>3 days apart).

8.2.4 *Paper IV*
The audit study population comprised of all the

neonates in the PH1 cohort, who died in-hospital (n=235) or were discharged alive after WLST (n=67).

8.3 Data collection

We retrieved data from the PH1:

A. Central hospital registry (*paper I-IV*)
B. List of death and WLST (*paper II-IV*)
C. Admission questionnaire (*paper II*)
D. BSI book and electronic database (*paper III*)
E. Medical patient file (*paper II-IV*)
F. Telephone follow-up (*paper II and IV*)

We obtained data from RH:

G. Neonatal department database (*paper I*)

A. Central hospital registry

All neonates admitted were identified and patient ID, sex, admission age, discharge age, discharge diagnoses according to The International Classification of Diseases, 10th revision (ICD10) (93), and discharge outcome were obtained. Further, for neonates with BSI data on central vascular catheter site and insertion period were registered.

Outcome at discharge ≤ 28 days was registered as either 1) discharged, 2) death, 3) WLST (defined as discharge with manual bagging by the family to await natural death at home) or 4) hospitalized (if the neonate was still in hospital at the age of 28 days)

B. List of death and WLST

To ensure complete data of neonatal death and WLST, the project group completed daily lists of cases according to information from clinical staff in the units, ward books, ward meetings and daily hospital conferences. The medical files of all possible cases were evaluated.

C. Admission questionnaire

A structured questionnaire was completed in Vietnamese upon admission. The predictors were selected according to previous infant risk scores for hospital referral in developing countries (61;64;65;94) and clinical experience within the project group. They covered socio-demography (ethnicity, maternal education, paternal education, and number of siblings), pregnancy-delivery (number of antenatal care visits, twin, normal delivery, gender, birth weight and maturity), neonatal history (difficulty in breathing, colour symptom, convulsions, lack of spontaneous movement, difficulty to wake up, difficulty to feed, type of feeding, abnormal stools, duration of symptoms, and transport duration), and clinical condition at admission (age, colour sign, temperature, impaired consciousness, respiratory failure, respiratory rate, grunting, chest retractions, and shock signs). The clinical doctor completed the questionnaire with the family. Mothers were preferred as interviewees. The questionnaire was translated form English to Vietnamese and back to English. Translations were compared and revised. The final Vietnamese version was pilot tested.

D. BSI registration

Blood culture results were obtained from the blood culture registration book and electronic database of The Department of Microbiology. For BSI, patient ID, sampling date, isolate and antibiotic susceptibility pattern were retrieved.

Laboratory methods

Blood culture was performed when severe clinical signs of septicaemia were present (often supported by other paraclinical indications) or in case of exchange-transfusion. A peripheral blood sample of 1-2 ml was drawn into a paediatric blood culture bottle (BACTEC, Becton Dickinson, New Jersey, US) after skin disinfection with povidone-iodine and alcohol. Bacterial growth was detected automatically (BACTEC 9,240/9,050 reader). Blood culture bottles were incubated for 6 days. If negative, a one-day subculture confirmation was carried out. If positive, cultures were examined by microscopy of Gram-stained smears and cultured on 5% sheep blood agar and MacConkey at 35°C moist air. If fungal infection was suspected, Sabouraud agar was included. The agar plates

were manufactured at the laboratory of PH1 from purchased ingredients (Becton Dickinson). Bacterial isolates were identified by conventional methods (95) using commercially available media (Bio Rad, Philadelphia, US). According to Gram-stain, antibiotic susceptibility of pathogens was tested on Mueller Hinton Agar (Becton Dickson) using disc diffusion (Oxoid, Hampshire, UK) for relevant antibiotics (96).

E. PH1 medical patient files
Medical files of all possible cases of death and WLST according to A. and B. were evaluated to ensure correct registration. If any discrepancies between registers and file, the file was superior. For each confirmed case, the file was reviewed and an English narrative was prepared with in-depth descriptions of relevant time-related events.

F. Follow-up
If WLST < 28 days of age, we attempted to call the family to register follow-up outcome at 28 days (dead/alive/unknown)

G. RH neonatal department database
Data were retrieved from RH neonatal department database for comparison. Data included ICD10 discharge diagnoses, sex, gestational age and birth weight. Data were obtained for a 10 year period and annual means were calculated.

8.4 Data management and analyses

All data were entered in Access or Epidata and analyzed in STATA IC 11. Double data entry was performed in a random sample of 10% of data and showed less than 5% discrepancy when compared (*papers II-IV*). Associations were analyzed using Chi-square test (*paper I-IV*) and multiple regression analyses (*paper II*). Two-sided p-values were calculated, and the significance level was set to 5%. Qualitative analyses were applied in one study (*paper IV*).

8.4.1 *Paper I*
In the comparative study, diagnoses were grouped in prematurity, infections, asphyxia and congenital malformations. Congenital malformations were sub grouped in oesophageal atresia, gastroschiesis, diaphragmatic hernia, heart disease and other congenital malformations. Furthermore, we classified relatively mild diagnoses defined as diagnoses which could probably be managed adequately at lower level of care.

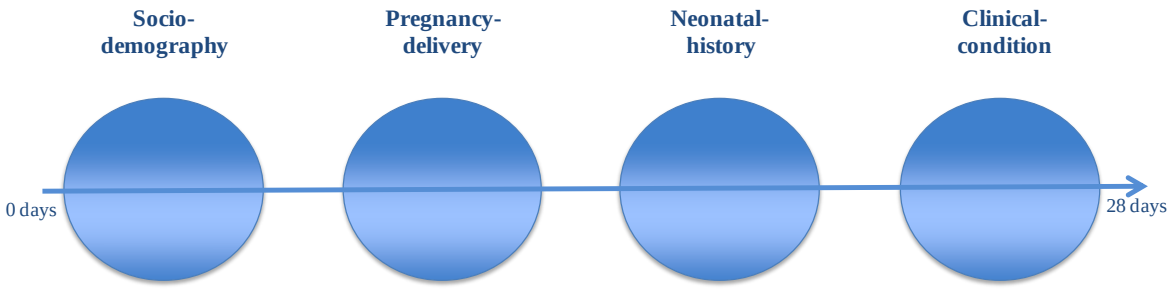
The diagnosis of prematurity was validated for very preterm (<32 gestational weeks, VPT) and very low birth weight (≤1,500g, VLBW) using the sub group questionnaire as reference. Gestational age was preferred. If unknown, birth weight was used. For the shared study populations (*paper I and IV*), the validity of diagnosis was evaluated, comparing ICD10 diagnoses assigned in the hospital to ICD10 direct death cause in the audit study (*paper IV*).

The neonatal population at PH1 was described and hospitalization rates of the diagnoses under study were compared to those of RH and the catchment population.

8.4.2 *Paper II*
In the predictor study, associations between pre-hospital predictors and the primary outcome (death), the secondary outcome (death or WLST), and tertiary outcome (WLST) were performed. Associations were analyzed using multivariate logistic regression analyses using backwards elimination if $p > 0.20$. The predictors were grouped according to the time they appeared; in socio-demography, pregnancy-delivery, neonatal history and clinical condition at admission (Figure 3). Each predictor was adjusted for other predictors within the same group and the predictors in the previous groups. Hence, first socio-demography predicators were adjusted within the group. Then pregnancy-delivery predictors were included in the model and adjusted within the group and for the remaining socio-demography predictors. Remaining predictor groups were entered in a similar manner. Gender, birth weight (≤ 1,000, 1,001-1,500,

1,501-2,500 and >2,500g) and admission age (0-1, 2-7 and 8-28 days) were kept throughout the model regardless of p-value. In the model including all groups, all predictors remaining were analyzed repeating backwards elimination to further reduce the number of predictors in the final model. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported. Possible interactions for gender and birth weight (>/≤ 1,500g) and trend test for rank scale predictors were investigated in the final model. If data on the outcome or predictor was missing, the neonate was excluded from analyses. Hence data imputation was not applied.

Figure 3
Predictor groups in logistic regression model



The predictors were grouped according to the time they appeared. Each predictor was adjusted for the predictors in the previous groups and within the same group

8.4.3 *Paper III*
In the BSI study, infections were grouped according to isolate, sample date, discharge diagnosis and neonatal discharge outcome. As part of the audit procedure (*paper IV)*, septicaemia relation according to ICD10 classification (direct or underlying death cause) was determined. Associations between isolate groups and septicaemia-related-death were analyzed.

8.4.4 *Paper IV*
In the audit study, procedures and report forms were pilot-tested and adjusted before commencing the study.

All death and WLST cases were audited in a structured procedure by the audit group, comprising two experienced neonatologists from NICU, a Danish paediatrician and a Danish professor of neonatology (Gorm Greisen). For each case the narrative and medical file was reviewed and a structured report completed at weekly meetings. Initially all the group met by internet and face-to-face meetings to get to know each other, the context and concept of audit as a shared open-minded process of investigating the events in a particular case. It was a dynamic process and any disagreements were discussed and consensus sought. Later the audit meetings were conducted in PH1 by 3 group members completing the audit report. The fourth member (GG) answered questions and commented on the report. Finally, the first three members decided if any adjustments should be made to the final report.

The audit comprised the following analyses:
A. Prognosis at arrival
The Vietnamese group members evaluated the prognosis at admission, if best available care was applied in PH1, in: >50% (relatively good) / ≤ 50% (relatively poor) / unknown survival chance. The chance of normal development in terms of growth, general health, and psychomotor function was categorized in a similar way. The Danish group members evaluated the prognosis at admission, if best available care was applied in RH.

B. Outcome at discharge
Outcome at discharge was assigned; dead or alive when leaving the hospital, and whether life – sustaining-treatment was withdrawn.

C. Cause of death
The cause of death/expected death was assigned according to two classifications systems. The direct and the underlying death cause were assigned according to ICD 10. The major death cause was assigned according to Child Health Epidemiology Reference Group hierarchical classification (CHERG) (2;97;98). From the top this classification ranks: major congenital malformation, tetanus, prematurity (gestational age <33 weeks or birth weight <1800 g), asphyxia, sepsis/ pneumonia, diarrhoea, and other.

D. Potentially avoidable risk factors
The risk factors were defined as avoidable within the existing context, without implementation of new technologies or major organizational changes. Furthermore, if avoided, the neonate would more likely than not have survived the neonatal period (>50% survival chance).

The audits were performed twice in a random sample of 10% of the cases and the resulting reports compared. Less than 5% discrepancy was revealed.

8.5 Ethical considerations
In Vietnam, the study was approved by The Scientific Review Board and Ethical Committee of the study hospital. In Denmark, The Danish Data Protection Agency approved the study. RH approved the use of the RH department database. The studies are not within the jurisdiction of The Danish National Committee on Health Research Ethics, Subcommittee on Developing Countries, which were explicitly asked. Family consent was obtained before completing data forms (*paper II and IV*). When relevant, a separate permission was obtained to follow up the family by telephone.

9. RESULTS
Characteristics of the study populations are shown below (table 1)

Table 1
Patient characteristics in paper I-IV (Median (interquartile range)* or %)

	Paper I (n=5763)	***Paper II*** (n=2196)	***Paper III*** (n=385)	***Paper IV*** (n=302)
Sex (boys/girls)	(55/45)	(59/41)	(60/40)	(60/40)
Birth weigth (g)*	na	2700 (2000-3100)	na	2400 (1900-3050)
Maturity (gestational weeks)				
Very premature (< 32)	na	4	na	32
Premature (32-36)	na	29	na	42
Mature (≥37)	na	67	na	26
Admission age (days)*	7 (2-17)	2 (0-8)	8 (1-14)	3 (0-4)
Length of stay (days)*	7 (4-15)	13 (7-23)	20 (6-29)	6 (1-9)
Major diagnoses at discharge #				
infection	62	47	64	9
congential malformations	15	23	14	9
prematurity	7	15	6	47
asphyxia	2	6	2	25
other	26	9	14	10
Neonatal hospital outcome				
discharge	70	58	45	nr
admission	25	30	38	nr
death	4	9	17	78
WLST	1	2	1	22

na (not available for the majority of the population), nr (not relevant), WLST (withdrawal-of-life-sustaining-treatment)
#Major diagnoses in central hospital registry. Paper I add up to 112%, because 12% had 2 diagnoses assigned

9.1 *Paper I*

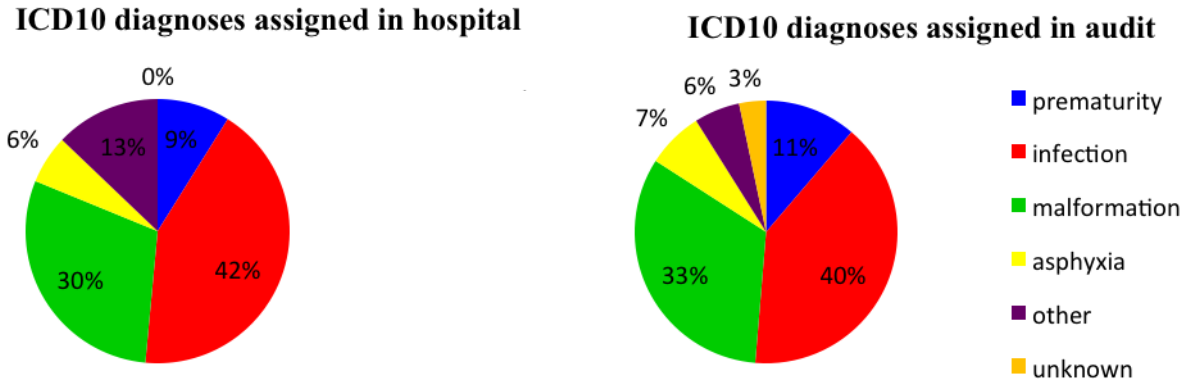
Characteristics

In the comparative study of the PH1 cohort of 5,763 neonates, 780 had 2 discharge diagnoses assigned. Mild diagnoses were assigned to 24% (data not shown). The neonatal case fatality rate was 4% (235/5,763). Another 1% (67/5,763) had WLST.

Validity of diagnoses

In 85% (286/336) the diagnosis of prematurity was assigned correctly to VPT or VLBW neonates. The diagnoses assigned in the hospital were also validated using the audit diagnoses (figure 4). No major discrepancies were revealed.

Figure 4
Comparison of ICD 10 diagnoses assigned in the hospital and in the audit study
(n=302, paper IV)



Hospitalization rates comparison

The hospitalization rates of prematurity, asphyxia and designated congenital malformations in PH1 and RH were compared. In PH1, the hospitalization rates were about 25 fold lower for prematurity (0.53 versus 13.24) and asphyxia (0.17 versus 3.99) compared to RH. These differences were the most pronounced. All of the hospitalization rates under study, including the congenital malformations, were significantly lower in the study hospital ($p<0.05$), when taking the difference in catchment populations into account (Table 2). Comparing PH1 hospitalization rates to rough estimates of the expected incidence rates in the catchment population also revealed striking differences, most pronounced for VP and severe asphyxia with a 40 fold lower registration in the hospital. For the congenital malformations the hospitalization rates were 3-20 times lower (*paper I*).

Table 2
Comparison of selected ICD-10 diagnoses in the PH1 and RH
The number of registered diagnoses and corresponding hospitalization rates per 1,000 live births in the catchment area

	PH1 Vietnam (n=5763)		**RH Denmark** (n=885)		
Diagnose	**Registered**	**/1000 live births**	**Registerd**	**/ 1000 live births**	**p-value**
Prematurity	385	0.53	384	13.24	<0.01
very premature	385*	0.53	206	7.06	<0.01
Asphyxia	120	0.17	116	3.99	<0.01
Malformations					
Oesophaus atresia	46	0.06	8	0.27	<0.01
Gastrochiesis	31	0.04	6	0.21	<0.01
Omphalocele	22	0.03	2	0.07	0.04
Diaphragmatic hernia	39	0.05	4	0.14	0.01
Heart Disease	222	0.31	65	2.23	<0.01

PH1 Paediatric Hospital no 1, catchment population 726,578 live births (2009)
RH (Rigshospitalet Denmark), annual means for a 10 year period, catchment population 29.161 live births (2009)
*Maximum estimate corresponding to all of the registered premature neonates (GA and BW was only available for a subgroup)

9.2 *Paper II*

Characteristics

The study of predictors comprised of a sub group of the PH1 cohort of 2,196 neonates (figure 1). Thirty percent were premature, but only 12% VPT in accordance with median BW of 2700 g (interquartile range 2,000-3,100). Compared to the entire PH1 cohort, the subgroup were admitted earlier and stayed longer in hospital (p<0.01).

Outcome

Compared to the entire cohort, significantly more died in this sub group (9% (n=198) vs. 4% (n=235) in the PH1 cohort; p<0.01) or had WLST (2% (n=51) vs. 1% (n=67 in the PH1 cohort), p<0.01). Among WLST, death was confirmed in 35 cases, while 2 cases were still alive. In 14 families, follow-up was not possible.

Predictors

The unadjusted odds ratios for death are shown in Table 3 in the appendix (12.1). Table 4 shows the adjusted odds ratios in the final model, including data on 168 deaths among 1,901 neonates (unbiased in regards to death compared to the full sub group). None of the socio-demographic predictors
including gender, ethnicity, and parental education were associated with death (p>0.20). Among pregnancy-delivery predictors, birth weight ≤1,500 g was significantly associated to death (p<0.01). Accordingly, the birth weight trend test was significant (p=0.03). None of the predictors related to neonatal history remained in the final model. Admission age >7 days predicted a significantly decreased risk of dying. Impaired respiration, circulation and consciousness at admission were also significantly associated with death, OR 2-5 (respiratory failure OR 5.19 (CI 2.89-9.30), shock OR 2.25 (CI 1.17-4.34) and lethargy-coma OR 3.03 (1.95-4.69), p<0.03. No interaction was found, when testing for birth weight and gender in the final regression model

Table 4
Adjusted risk of death for predictors in final model
(Odds Ratios (OR) and 95% confidence intervals (CI))

PREDICTOR	OR (CI)	p
Gender		
Male	1.00	
Female	0.99 (0.68-1.44)	0.97
Birthweigth (gram)		**0.01**
≤1000	4.34 (1.46 - 12.96)	**<0.01**
1001-1500	2.13 (1.25-3.63)	**<0.01**
1501-2500	1.20 (0.78 - 1.84)	0.40
>2500	1.00	
Admission age (days)		**<0.01**
0-1	1.00	
2-7	1.14 (0.71 - 1.81)	0.59
8-28	0.43 (0.25 - 0.75)	**<0.01**
Color sign		**0.01**
Pink	1.00	
Jaundice	1.32 (0.77 - 2.25)	0.30
Cyanosis	2.48 (1.46 - 4.21)	**<0.01**
Pale	2.07 (0.92 - 4.71)	0.08

PREDICTOR	OR (CI)	p
Consciousness		
Awake	1.00	
Lethargy-coma	3.03 (1.95 - 4.69)	**<0.01**
Respiratory Failure*		
No	1.00	
Yes	5.19 (2.89 - 9.30)	**<0.01**
Grunting**		
No	1.00	
Yes	0.65 (0.34-1.24)	0.19
Retraction**		**<0.01**
No	1.00	
Moderate	2.05 (1.29 - 3.25)	**<0.01**
Severe	3.18 (1.63-6.21)	**<0.01**
Shock***		
No	1.00	
Yes	2.25 (1.17-4.34)	**0.02**

*Defined as gasping/prolonged apnea/intubation/bagging
** If no respiratory failure
*** Defined as minimum 2 out of 3
(tachycardia/bradycardia, prolonged capillary refill time, weak pulse)

The main findings were similar when performing the analysis for the secondary (composite) outcome death/WLST and the tertiary outcome WLST alone.

9.3 *Paper III*

Characteristics

In the BSI study of 2,202 blood cultures, 399 were positive (n=385 patients). Among neonates with BSI, only 16% were diagnosed as early onset (≤3 days of age at sampling), whereas 84% were diagnosed as late onset (>3 days of age at sampling). At the time of sampling, 3% had a central vascular catheter. The discharge diagnosis was infection in 64% of neonates, in 34% of these the diagnosis was septicaemia. Of the 64 neonates who died, 62 died in relation to septicaemia.

Isolates

The majority of BSI isolates were known pathogenic and Gram-negative (table 5).

Table 5
Distribution of isolates and their pathogenicity among BSI
(n=399) in all neonates (n=385) and in the neonates who died in relation to septicaemia (n=62)

Pathogenicity	Isolate	All BSI	Neonatal deaths
Known	***Klebsiella*** spp	78	19
	Acinetobacter spp	58	10
	Escherichia coli	21	5
	Enterobacter spp	16	5
	Morganella spp	8	2
	Pseudomonas spp	6	1
	Proteus spp	3	0
	Burkholderia spp	2	0
	Staphylococcus aureus	11	2
	Enterococcus spp	5	1
	Streptococus spp	3	1
	Candida spp	13	3
Potential	***Staphylococcus*** coagulase negative	175	13
Total		399	62

BSI (blood stream infections)
14 cultures were duplet samples in neonates having 2 BSI diagnosed with different organisms isolated at different times

Septicaemia related mortality
The septicaemia related mortality was 16% (62/385). The groups in table 6 on next page had significantly different mortality risks ($p<0.01$). Gram-negative bacteria other than *Acinetobacter* spp carried the highest mortality.

Table 6
Association of isolate group and septicaemia related mortality
(n=62) (OR and CI)

Isolate	OR	CI
No confirmed Blood Stream infection	1.00	
Staphylococcus coagulase negative (SCN)	1.54	0.84-2.83
Acinetobacter spp (Acb)	3.95*	1.93-8.09
Other Gram-negative baceteria (GN)	6.26*	3.96-9.89

*$p<0.001$

Antibiotics susceptibility
Susceptibility to antibiotics empirically applied in the hospital was limited, particularly among Gram-Negative bacteria (table 7).

Table 7
Bacteria susceptibility in 399 BSI and empiric antibiotics recommendation
(% (sensitive/total cultures))

Antibiotics and indication	Gram-negative species						Gram-positive species			
	Kleb (n=78)	Acinetob (n=58)	E Coli (n=21)	Enterob (n=16)	Morg (n=8)	Pseudo (n=6)	CoNS (n=175)	SA (n=11)	Enteroc (n=5)	Strep (n=3)
1 line										
Ampicillin	0	15	14	7	13	0				
Cefotaxime	14	18	42	38	48	17				
Gentamicin	15	50	43	38	25	52	34	72	0	0
2. line										
Ceftazidime	29	29	58	50	50	67				
Ciprofloxacin	29	78	52	38	25	67				
Pefloxacin	12	73	52	44	14	17	37	86	0	0
2-3. line										
Vancomycin							99	100	100	100
Cefepime	19	42	40	47	43	67				
Timentine*	18	41	48	38	29	67				
3. line										
Meropenem	98	57	100	100	100	100				
Imipenem	96	59	100	88	100	83				
SA suspicion										
Oxacillin							16	45	0	67
Rifampicin							84	100	60	100

*Timentine = ticarcillin/klavulanova acid

Kleb (*Klebsiella* spp), Acb (*Acinetobacter* spp), Enterob (*Enterobacter* spp), Morg (*Morgenella* spp), Psudo (*Pseudomonas* spp),

CoNS (coagulase negative *Staphylococus*), SA (*Staphylococus* aureus), Enteroc (*Enterococus* spp), Strep (*Streptococus* alpha hemolytic)

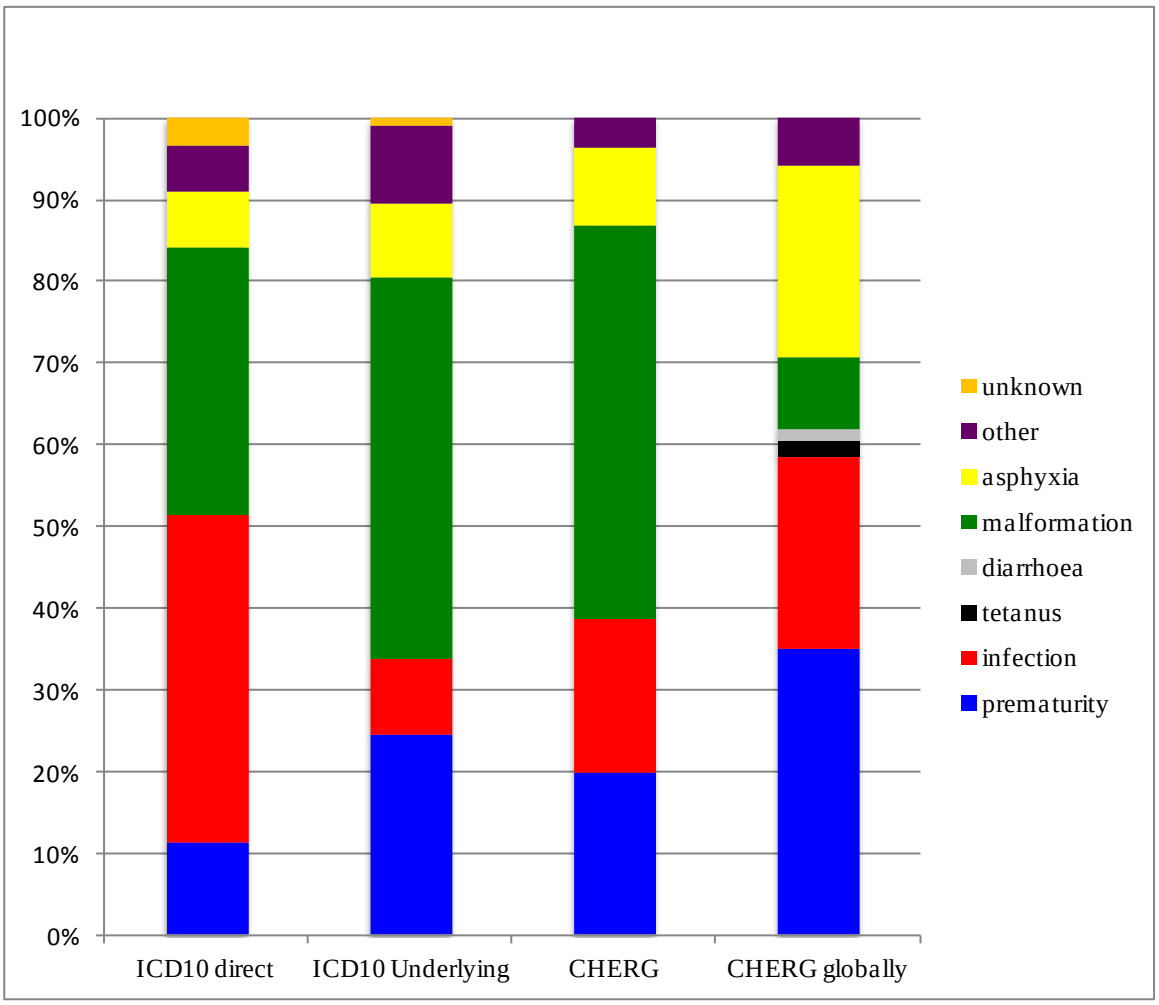
9.4 *Paper IV*

In the audit study, among 302 cases 235 died in the hospital and 67 were discharged after WLST. In 38 of the 67 cases, death at home was confirmed, while 2 were alive at 28 days of age. In the remaining 27 cases, follow up was not possible.

Cause of death

According to both classification systems, the major causes of death/expected death were congenital malformations, prematurity and severe infection (figure 5).

Figure 5
Distribution of death/expected death causes in the hospital (n=302)
According to ICD10 classification (direct and underlying death causes) and CHERG classification of major cause of death in PH1 and global estimates (4 million annual deaths in year 2000)



Malformation, infection and prematurity caused more than 80% of the deaths/expected deaths (WLST) in the hospital, according to both ICD10 and CHERG. Compared to global CHERG estimates, malformations were more frequent and prematurity was less frequent.

Prognosis in PH1 and RH

Prognosis at arrival was evaluated for PH1 and RH, given the best possible treatment available in each of the two settings. As expected the prognosis was better in RH, where 61% would have had a relatively good prognosis compared to 24% in PH1.

Table 8
Prognosis at arrival evaluated in PH1 and RH settings
(n=302), (n (%)).

Prognosis	PH1	RH
Unknown	41 (14)	68 (23)
Releatively poor	190 (63)	50 (17)
Relatively good	71 (24)	184 (61)

PH1 (Paediatric Hospital no1), RH (Rigshospitalet, Denmark)
Unknown: either prognosis for survival or development was evaluated unknown. Relatively poor: prognosis for survival or development was evaluated ≤50%, and none of them evaluated unknown. Relatively good: both prognosis for survival and development were evaluated >50%.

Potentially avoidable risk factors
We identified 6 potentially avoidable in-hospital risk factors in 85% (60/71) of the neonates with a relatively good PH1 prognosis at arrival.

Table 9
Risk factors among neonates with relatively good prognosis (n (%)).
Relatively good prognosis defined as >50% chance of survival and normal development at arrival (n=61)

Dealyed recognition and/or response to danger signs	30 (42)
Suboptimal internal transfers	26 (37)
Family and/or medical staff misperception of prognosis	25 (35)
Nosocomiel infections	24 (34)
Suboptimal septicaemia management	17 (24)
Shortage of equipment usually available	12 (17)

10. DISCUSSION

This thesis describes neonatal mortality in a tertiary paediatric hospital. Conditions known to be major causes of neonatal mortality globally (*paper I and III*) and risk factors of neonatal mortality – pre-hospital (*paper II*) and in-hospital (*paper IV*) - were described in order to improve hospital management and ultimately decrease neonatal mortality.

We do not know how Vietnamese families perceive the needs of the family and their neonates, if born with any of the conditions investigated. They may not want their neonates to survive at any cost, considering the short and long term perspective in this resource-limited setting. Development and long term deficits are known concerns in children surviving neonatal morbidity. From an utilitarian point of view other stakeholders could also be taken into account, such as the health care system and the society. It is an underlying assumption in this thesis, however, that we want to try to save neonatal lives.

10.1 Discussion of findings paper I-IV

10.1.1 PH1 neonatal population *(paper I)*
Comparison of hospitalization rates
Prematurity, asphyxia and designated congenital malformations were under represented in PH1, compared to both hospitalization rates at RH and to rough estimates of catchment population incidence rates. In contrast, mild conditions accounted for almost a quarter of the admissions.

Methodological considerations
The validity of diagnoses was high in the two sub groups examined, VP/VLBW and the audit study

population. However, the general validity of the ICD10 diagnoses assigned in the hospital may be questioned (99-101) .

We assumed RH to be a comparable tertiary hospital in a developed setting and to have a neonatal population less prone to selection bias. In RH, high risk pregnancies are referred before delivery, the catchment population is smaller, neonatal intensive care transport is provided and more diagnostic and treatment options are available. Furthermore, in Demark health care is free (also in practice), the support to children with special need is extensive, there is no family size policy, the care of the elderly is mainly a public responsibility, and families and staff may be stronger advocates for full treatment of vulnerable neonates.

Whether the two settings are comparable may be disputed, since it requires crude incidences in the catchment populations to be roughly steady over regions. However, we used conservative estimates and the differences we found between the two settings are likely to be minimum differences, since asphyxia and prematurity crude incidences are expected to be higher in Vietnam (11;21). We also compared the PH1 population directly to the catchment population using rough incidence estimates derived from a literature search. Local estimates were not available, but when available, estimates were adapted to the region or context. A systematic review of the literature would have been ideal.

Suboptimal utilization of PH1
Conditions usually requiring specialized care seemed underrepresented in PH1, while relatively mild conditions were frequent. Most patients in this busy hospital were referred from other health care facilities, which could probably have managed the relatively mild conditions adequately and it would be interesting to explore the reason and circumstances of these referrals. This hospitalization pattern may reflect suboptimal utilization of specialized neonatal care, a challenge that may not be unique for this hospital.

PH1 cannot cover the need for specialized care in all of South Vietnam. The population and geographical area are huge, the capacity was overloaded already and not all the neonatal beds had intensive care capacity. To cover the need of specialized neonatal care in South Vietnam, PH1 utilization could be improved, but other providers are necessary, also at the provincial level.

10.1.2 Pre-hospital predictors of death *(paper II)*

Predictors
In a subgroup of the PH1 cohort, pre-hospital predictors of hospital death were examined. We focused on the most vulnerable neonates, including neonates from ER, NICU and SICU. We found no significant socio-demographic predictors. Notably parental education, gender and ethnicity were not associated to death. We only examined associations, once admitted to the hospital, but socio demographic characteristics may influence the admission selection to the hospital. Accordingly, ethnicity and education has been shown of importance for neonatal and child survival in other settings (102-106). Male preference has caught attention in Vietnam, due to the cultural male preference in the region (107-110) and increasing imbalanced gender birth rate in the country (111). The economic situation of the family would have been relevant to investigate (1;105;112;113), either as household income or asset index. However, asking was perceived inappropriate and replies unreliable. (Average is perceived as the correct answer, since you are not supposed to stand out of the crowd as either rich or poor).

As expected, vital signs at admission were of importance. Impaired respiration, circulation and consciousness were significantly associated with death. These findings could contribute to development of a clinical risk score at admission, to be examined by diagnostic tests. Accordingly,

early warnings scores are the focus to optimize hospital management in general, not only for neonates.

Outcome
No death or WLST occurred outside the inclusion wards. As primary outcome we chose confirmed death in the hospital. Because of the poor follow-up we did not include the deaths confirmed at follow-up in the primary outcome. All deaths and WLST were included in the secondary outcome. To examine if the groups of WLST and death differed, WLST alone was examined as tertiary outcome. Using the secondary and tertiary outcome in the model did not change the main findings.

Methodological considerations
There are several considerations in the methods applied. Regarding power of the study, the calculated sample size was achieved, but for some of the predictors the prevalence was lower than expected. As for patient enrolment, 4 neonates who died on arrival could not be included for administrative reasons in the hospital. We did not randomize patients in SICU, which would have reduced the risk of selection bias. The level of significance, was not Bonferroni-corrected to the multiple testing, but no p-values of the significant associations were borderline and the risk of type I error (false positive findings caused by chance) is less likely.

We chose a model including the temporal dimension, which was inspired by the theory driven causal diagram concept (114;115). After much consideration, this seemed to be the most meaningful way of confounder adjustment. We did not choose a data driven model, where predictors are included according to the unadjusted p-values. The analyses were conducted using logistic regression, which does not take potential drop-outs into account. However, censoring in the present study was not independent of outcome, which is one of the assumptions in event time analysis e.g. Cox regression. The WLST neonates were censored because of a high risk of in-hospital death, while the discharged neonates had a low risk per se. The analysis of the secondary outcome (death or WLST) may be viewed as a sensitivity analysis of the primary outcome (death) including the WLST neonates, who we believe would have died in-hospital if they were not discharged. This did not affect our main results.

10.1.3 BSI *(paper III)*
The majority of BSI were late onset, which was likely due to admission bias.

Isolates
Among the PH1 cohort, in 18% of the blood cultures performed BSI were confirmed. The majority were known pathogenic. Among these, Gram-negative bacteria were the most frequent. No *Streptococus* group B was isolated. Hence the BSI pattern resembled other resource-limited settings (15;16;75-79).

Antibiotic resistance
In agreement with studies from other resource-limited settings, antibiotic resistance was frequent (116-119), including resistance against antibiotics applied in the hospital (120;121). Accordingly, revision of the hospital guidelines should be considered to target BSI and prevent further resistance development (122;123). Carbapenems could be considered as first choice if severe clinical signs of septicaemia, especially if Gram-negative origin is known. Transmission from the environment via care providers is a major concern and hygienic precautions are important.

Clinical relevance of BSI
BSI was a surrogate parameter for the clinical condition of septicaemia. Lack of supportive clinical and paraclinical data limits the clinical relevance of our findings. Furthermore, it is difficult to determine whether BSI is the cause or the consequence of severe illness, since sick neonates are at high risk of infection and prone to have blood cultures performed. However, the

indication for performing blood culture was severe clinical signs of septicaemia.

Septicaemia related mortality
Gram-negative bacteria carried the highest septicaemia related mortality. *Acinetobacter* spp is known to be less pathogenic than other Gram-negative bacteria such as *Klebsiella* spp and *Escherichia* coli, but cause increasing resistance problems (124-127).We evaluated which of the deaths in this study population were related to septicaemia using death cause assigned according to ICD10 (*paper IV*). Other applicable methods to determine the relation were time span between sample and death (< 6 days apart) (15), ICD10 discharge diagnoses assigned in the hospital and CHERG death cause assigned (*paper IV*). It limits our findings, that our analysis was not adjusted for possible confounding conditions such as other major death causes.

10.1.4 Death causes and risk factors *(paper IV)*
Causes
The major causes of death/expected death were congenital malformations, prematurity and severe infections in both classification systems, underlining the robustness of the findings. Compared to a rural community study in North Vietnam, the proportion of asphyxia and prematurity among death causes were 2-3 fold lower in PH1 (38).

Prognosis at arrival
Compared to RH, less had a relatively good prognosis at arrival (>50%) evaluated in the setting of PH1 in terms of survival and development. This is expected, reflecting the different possibilities in management in a high and a low income country. The finding may also reflect different perceptions of what defines a relatively good prognosis (128). Notably, 17% also had a relatively poor prognosis in RH, reflecting the severity of the case-mix in the study hospital. In the PH1 prognosis fewer cases were classified as unknown prognosis compared to RH, probably reflecting less strict diagnostic criteria and a better understanding of the context. Hence, PH1 doctors are used to working with limited diagnostics and may settle for a diagnosis in spite of uncertainty. Furthermore, for PH1 doctors it may be easier to assign diagnoses, since they know the clinical setting better including, for example, the usual presentations and disease prevalences.

Potentially avoidable risk factors
Among the 71 neonates with a relatively good prognosis in PH1, we identified 6 potentially avoidable risk factors relevant to 85% (60/71) of cases examined, which could be addressed without implementation of new technology or major organizational changes. The risk factors were: delayed recognition and response to danger signs, suboptimal internal transfers, nosocomial infections (diagnosed 48 hours after admission), suboptimal septicaemia management, shortage of available equipment and misperception of prognosis. We considered it as misperception of prognosis, when the audit group found the treatment to be more restrictive than the prognosis indicated. It can be disputed whether this was truly misperception or that the accepted threshold of treatment differed between the audit group and family or treating staff. Furthermore, study participation may have influenced the PH1 prognosis assigned in the audit and the more optimistic RH prognosis may have spilled over to PH1 evaluation of prognosis. If so, maybe study participation in itself could impact clinical management and mortality in the hospital.

End of life decisions
End of life decisions is a well known dilemma in neonatal care, both in developed and developing countries (50-56). In practice the activity level of care constitutes a spectrum from full active care to WLST, where the patient dies instantaneously or can live for some time. In the hospital, the decision to restrict treatment was often taken gradually, not transparently and not well documented. In some cases the family and doctors

disagreed. There are no ethical or legal guidelines on this issue in the hospital or in Vietnam.

Methodological considerations
We chose to include WLST, in spite of the uncertainty of follow-up, as these cases were expected to die and would have been kept in hospital in other cultural settings. Furthermore, WLST was also practiced in neonates dying in the hospital. The method of mortality audit is particularly used in the area of perinatology, including criterion based audits. In the complex management preceding neonatal death, a strict criterion based approach is more difficult, but when possible we applied national (129) and hospital (120;121) guidelines as broad references. The lack of neonatal indicators in The National Indicator Project in Denmark also reflects these difficulties. Consensus was sought in the discussions, which may have affected the findings (130), including prognosis in the two settings. We evaluated the reliability of the audit procedure high in a random sample of re-audits.

10.2 General considerations and perspectives

10.2.1 External validity
The neonatal mortality rate in the catchment population was unknown. It would have been relevant to put the findings in our hospital population into perspective. The external validity of our findings depends on the comparability of the populations and hospitals. Specialized hospitals like the study site, exist throughout the developing world and pre-hospital selection of neonatal patients is likely to be a general concern. Our findings may be relevant to other specialized paediatric hospitals existing in Vietnam and other resource-limited settings

PH1 population selection
The admission process in our hospital from the huge catchment population of more than 700,000 live births is obviously complex. The neonatal population of PH1is likely to be highly selected for a number of reasons other than medical; most importantly the neonatal population constitutes only 0.8% of the huge catchment population. Furthermore, the hospital does not offer obstetric care and various circumstances may influence the decision to present to the study hospital. Poor prognosis (as judged by staff or family) (14;21;131), death, misdiagnosis, transportation limitations, lack of treatment options in PH1, limited support for families of children with special needs, the 2-children policy and hidden user fees despite a policy of free paediatric care may all contribute to not being selected for specialized care (3, 5, 13). Health seeking behaviour of the family may also play an important role.

Other specialized care providers
Three other hospitals provided specialized care for South Vietnam, all located in Ho Chi Minh City. Even considering these hospitals, the hospitalization numbers in the study hospital remain low for the catchment population. The maternity hospitals admit neonates delivered in their hospital only, leaving 90% of the catchment population for the paediatric hospitals. In this group only 1.3% was admitted. This rate was 8-fold lower than the hospitalization rates in Denmark and lower than the rates of other developing countries (132-134). However, variations in catchment populations and definition of specialized care allow only rough comparisons of trends.

The need for specialized care
Specialized care in the provinces was very limited. In 30/32 provinces within the catchment area, the highest level of neonatal care available was basic care in 10 provinces, intermediate care in 19 provinces and intensive care in 1 province (PH1) (135). Furthermore, the mean NMR was more than 3 fold higher at the basic care level than at the intensive care level. According to current official recommendations, secondary general hospitals in the provinces should provide specialized neonatal care (136).

Access to specialized care could increase neonatal survival. If the number needed to treat to save the life of 1 neonate is roughly set to; 1-2 providing surgery for malformations (like oesophagus artresia and congenital diaphragmatic hernia), 2-3 providing surfactant for prematurity (respiratory distress syndrome) and 10 providing cooling for asphyxia, these interventions are essential and cost-effective.

The 150 neonatal beds in PH1 are far less than the estimated required minimum of 726 beds for specialized neonatal care (1- 9 per 1,000 births). This is a conservative estimate depending on the size of the catchment population and definition of specialized care (137-142). To increase access to specialized care, availability of existing tertiary care and upgrade of secondary care is important. Ideally in hospital settings providing both obstetric and paediatric care.

10.2.2 Integrity of neonates

The perspective of neonatal integrity is important to understand global neonatal mortality. According to some anthropologists, in many cultures individual integrity must be gained gradually throughout childhood. In Vietnam child birth is not celebrated until the infant is 1 month old ("Rite of the first full moon"). An infant is usually not named before this time and a neonate is not regarded as a full member of the family. A dying neonate is sometimes brought home from the hospital for the soul to feel warm and a sense of belonging in the hope the soul will soon reincarnate as another baby. The body or ashes are laid to rest in the temple without a name. Sometimes a small ceremony is held, but in privacy and not a spectacular event with many visitors as it is custom in adult funerals. In PH1, we often discussed the rights and the fairness to the family, hospital and society. But the rights and the needs of the neonate were rarely explicitly stated as a major concern. The official registration of birth and death is the responsibility of the family. This may reflect or contribute to questioning the full integrity of neonates. It can also be questioned whether we fully respect the integrity of our neonates in resource-rich settings, if we go too far to preserve neonatal lives. The balance is difficult.

10.2.3 Changing research paradigm

Traditionally, research in international health has focused on community settings. However, urbanization is increasing rapidly throughout the world and in less developed regions the majority live in cities, most in large cities with more than a million inhabitants. Furthermore, the projected population growth is expected to be absorbed in cities (143). To serve these cities, large and mega hospitals are built, which are finance and human resource demanding. This may change the paradigm of international health research to include more hospital settings like the study site.

11. CONCLUSIONS

We prospectively investigated neonatal mortality in a specialized paediatric hospital in Vietnam, studying a cohort of 5,763 neonates admitted in a 12 month period.

In this setting, prematurity, asphyxia and congenital malformations seem to be underrepresented, compared to a similar hospital in Demark and to rough catchment population estimates. These conditions are major causes of neonatal death globally. In contrast, mild conditions were frequent.

In the cohort, we verified BSI in 18% of cultures. In total, 385 neonates were diagnosed with BSI. The majority were late onset and caused by known pathogenic species, of which Gram-negative bacteria comprised the vast majority. No *Streptococcus* group B were identified. The septicaemia related mortality was highest among neonates with Gram-negative BSI. Resistance was common.

Among a sub group of the PH1 cohort (n=2196), notably gender, ethnicity and parental education were not among the pre-hospital predictors associated to death in the hospital. Clinical condition at admission, including impaired respiration, circulation and consciousness, were associated with death. Thus, our findings support the importance of basic vital parameters to identify neonates in particular need of active early management.

The major causes of death/expected death were congenital malformation, prematurity and severe infections in the hospital cohort. Among the neonates with a relatively good prognosis at admission, 6 potentially avoidable in-hospital risk factors were identified, which could be addressed without implementing new technologies or major organizational changes. The risk factors were related to management of general danger signs, septicaemia, internal transfer, equipment, and misperception of prognosis.

12. IMPLICATIONS

12.1 Implications for clinical practice

Implications for clinical practice if we want to improve neonatal survival:

- Increased access to specialized care for vulnerable groups of neonates, including neonates with congenital malformations, asphyxia and prematurity. This could be achieved by improved utilization of existing specialized tertiary level care and upgrade of secondary general hospitals in the province, in accordance with current official recommendations
- Improvement of early hospital management. Possible interventions are inter-hospital telephone briefing before referral and request of neonatologist supervision if the clinical condition at admission is impaired.
- Strengthening of hygienic precautions, systematic surveillance of neonatal blood stream infections, and evaluation of present antibiotic guidelines to improve infection management in the hospital.
- Establishing a group to investigate possible interventions in the hospital to complete the mortality audit cycle, including management of restricted treatment and perception of poor prognosis.
- Considering regular structured mortality audit practice.

12.2 Implications for future research

Vietnamese paediatricians and public health doctors should come together and agree on a prioritized research agenda. Based on our research, we suggest the following questions to be considered:

- What is the population based neonatal mortality rate in Vietnam?
- What is the current level of care at secondary and tertiary hospitals in South Vietnam?
- How to develop and test an early warning score for neonatal admissions to the hospital?
- How to evaluate other improvements in early management in the hospital?
- What is the burden of septicaemia in the hospital?
- How to evaluate the effect of audit? Including evaluating implementation of interventions addressing the risk factors we identified

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APPENDIX 1

Original paper I

APPENDIX 2

Original paper II

Predictors of Neonatal Death in a Pediatric Hospital in Vietnam

Alexandra Yasmin Kruse[1], Binh Ho[2], Cam Ngoc Phuong [2], Henrik Ravn[3,4], Lone Graff Stensballe[3,5], Gorm Greisen[3,6] and Freddy Karup Pedersen[1, 2, 3]

[1]The International Child Health Research Unit, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark
[2]Neonatal Intensive Care Unit, Paediatric Hospital 1, Ho Chi Minh City, Vietnam
[3]Statens Serum Institute, Copenhagen, Denmark
[4] The Faculty of Health and Medical Science, Copenhagen University, Copenhagen, Denmark
[5]The Department of Paediatrics and Adolescent Medicine, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark
[6]Department of Neonatology, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Correspondence: *Alexandra Y Kruse, International Child Health Research Unit, 4072, Juliane Marie Center, Rigshospitalet, 2100 Copenhagen Ø, Denmark, Tel: +45 35453864, email: alexandra.kruse@dadlnet.dk*

Abstract

Objective. We explored predictors of neonatal (≤ 28 days) hospital death in Vietnam. *Methods*.
A prospective cohort study in a paediatric hospital from February 2009 to February 2010, comprising the most vulnerable neonates (all neonates from Emergency Room and Neonatal Intensive Care Unit and every second from Neonatal Semi-Intensive Care Unit). As part of the admission procedure, the doctor and family completed a questionnaire on possible predictors of neonatal death. Predictors were grouped into categories: socio-demography, pregnancy-delivery, neonatal-history and clinical-admission-condition, and analyzed using multivariate regression. *Results*. Of 2196 neonates included (missing < 2%), 198 died (9%). The study population was characterized by: 59% males, 33% premature, median birth weight 2700g (interquartile range 2000-3100), and median admission age 2 days (interquartile range 0-8*)*. Ethnicity, gender, and parental education were not associated with death. Impaired respiration, circulation, and consciousness at admission were associated with increased risk of death; adjusted odds ratios (95% CI): 5.19 (2.89-9.30), 2.25 (1.17-4.34) and 3.03 (1.95-4.69) ($p < 0.03$). *Conclusions* Notably, we found no socio-demographic predictors of death. The study supports the importance of vital signs at admission. The benefit of systematic use of these should be investigated further to improve early hospital management and neonatal survival.

Abbreviations and Definitions

Neonate: age ≤ 28 days; Low birth weight (LBW): < 2500g, Very low birth weight (VLBW): ≤ 1500 g; Preterm (PT): Very preterm (VPT): gestational age < 32 weeks; Neonatal Mortality Rate (NMR): deaths ≤ 28 days of age / 1000 live births, Withdrawal-of-life-sustaining-treatment (WLST) discharged alive on manual bagging and awaiting natural death.

Key words

Developing countries, hospital, lower middle income country, morbidity, mortality, neonate, newborn, predictor, Vietnam

Contributions

All authors contributed to study planning, discussion and interpretation of data and approved the final version of the manuscript. Data collection and data management was done by AK and BH.
Statistical analysis was conducted by AK, supervised by HR. First manuscript was drafted by AK.

Funding

This study was supported by grants from The Danish International Development Agency Danida, Christian the Xth Fund, Dagmar Marshall Fond, Torben Iversen Travel Fund and Copenhagen University Faculty of Health Science PhD Travel Fund

Conflict of Interests

The authors declare no conflict of interest.

1. Introduction

Among the millions of children dying annually (< 5 years of age), the vast majority dies in the developing world. Neonates (≤ 28 days of age) constitute more than 40% of all child deaths [1,2]. The reduction in neonatal mortality lags behind and hampers the fulfillment of The Millennium Development Goal to reduce child mortality [3]. Globally, infection, prematurity, and asphyxia cause more than three quarters of neonatal deaths [2,4,5].

To combat infant mortality in developing countries, clinical risk scores have been developed to guide referral of infants, including neonates, to hospital level care [6-9]. However, predicting neonatal mortality risk at the time of admission to improve early hospital management has had less attention. This is particularly relevant in emerging economy countries like Vietnam, where the majority of neonatal deaths presumably occur in hospitals.

In Vietnam an estimated 17.000 neonates die annually [3]. However in the absence of a valid vital registration system, mortality in Vietnam is probably under reported, particularly among neonates [10-14]. The current knowledge about neonatal morbidity and mortality is limited and rely on estimates and data modeling. According to global estimates the neonatal mortality in Vietnam accounts for more than half of the child mortality [3,10,15]. Reported neonatal mortality rate (NMR) is 12/1000 live births compared to 2-4/1000 live births in Europe and up to 50/1000 live births in Sub Saharan Africa [15]. Vietnam has now risen to a lower middle-income country and has achieved substantial reductions in child mortality [10], but to a lesser extent for neonates [16]. Almost 90% of women give birth in health care facilities [10] and the majority is assumed to remain hospitalized the first days after delivery. As this is the most vulnerable period [2], most neonatal deaths are anticipated to occur in hospital.
To our knowledge no peer-reviewed reports on neonatal hospital mortality is available from Vietnam. The aim of the present study was to identify predictors of neonatal death, in order to improve the early hospital management and neonatal survival ultimately.

2. Materials and Methods

2.1 Setting. The present study was undertaken at The Paediatric Hospital Number 1 (PH1) in Ho Chi Minh City, Vietnam. It is a 1200-bed tertiary referral hospital for South Vietnam admitting 86,000 children annually (about 2/3 from the provinces and 1/3 the city), the vast majority (approximately 95%) are referred from other health care facilities. It is a specialized paediatric hospital and hence does not provide obstetrical care. The 150-bed neonatal department comprises units of basic, semi-intensive and intensive care. Bed occupancy was 154% in the study period. The neonatal care included exchange transfusion, surfactant replacement, ventilator support (including high frequency ventilation) and surgery. The care was the most advanced provided in the country.

In 2009, the 726,578 live births in South Vietnam (total population 42 millions) constituted the potential catchment population, corresponding to approximately half of the deliveries in the country [17].

2.2. Patients. During a 12 months study period from February 2009 – February 2010, a prospective cohort subgroup was established of neonates (≤ 28 days of age) admitted to the following units: emergency room (ER), neonatal intensive care unit (NICU) and semi-intensive care unit (SICU). Neonates admitted to the basic neonatal care unit (NCU) only were not included. All eligible neonates were included from the ER and NICU. From SICU every second eligible neonate was included from the admission book kept by the clinical

nurse in charge. This selection was applied to focus on the most vulnerable neonates, to reduce workload in the department, and to maximize data completion. Patients were included when eligible the first time and only once (because of internal transfers, patients could be assessed for eligibility more than once).

Inclusion criteria: neonate, informed consent, admission to the ER, NICU or SICU.
Exclusion criteria: previously enrollment, unknown birth date, and conjoined twins.

Neonates dead on arrival to the hospital were registered separately.

2.3 Data collection

Outcome

Discharge age and status was obtained from the central hospital registry. Status at discharge ≤ 28 days was registered as either discharged, dead in hospital, or discharged alive after withdrawal-of life-sustaining treatment (WLST). Status was registered as hospitalized, if the neonate was still admitted in the hospital at 28 days of age. To ensure correct registration of death and WLST, these cases were also listed separately by the project group throughout the study period according to information from clinical staff in the units, ward books, ward meetings and daily clinical hospital conferences. The medical files of all possible cases were evaluated. For WLST < 28 days of age, we attempted to call the family, to register whether the neonate died within 28 days of age.
WLST was defined as discharged on manual bagging and awaiting natural death. This procedure was applied, when the staff and family perceived the prognosis too poor and wished for the neonate to die at home.

The primary outcome was death in the hospital ≤ 28 days of age.
The secondary outcome was death in the hospital or WLST ≤ 28 days of age.

Predictors

A structured questionnaire on possible predictors was completed in Vietnamese. The predictors were grouped in socio-demography (ethnicity, maternal education, paternal education, and number of siblings), pregnancy-delivery (number of antenatal care visits, twin, normal delivery, gender, birth weight and maturity), neonatal history (difficulty in breathing, color symptom, convulsions, lack of spontaneous movement, difficulty to wake up, difficulty feeding, type of feeding, abnormal stools, duration of symptoms, and transport duration), and clinical condition at admission (age, color sign, temperature, impaired consciousness, respiratory failure, respiratory rate, grunting, chest retractions, and shock signs). The receiving doctor scored the clinical condition, as part of the admission procedure for all neonates in the study period. If the neonate was considered eligible, the treating doctor interviewed the family and completed the rest of the questionnaire. Mothers were preferred as interviewees.

The questionnaire was translated from English to Vietnamese and back to English, and translations were compared and adjusted. The final Vietnamese version was pilot tested.

Other characteristics

From the central hospital registry discharge diagnoses were also extracted. The diagnoses were assigned according to The International Classification of Diseases 10^{th} revision (ICD10) [18] by the doctor discharging the infant. If more diagnoses were relevant, the doctors were instructed to assign the most important diagnoses including the underlying disease and important complications.

Informed consent was obtained from all families before inclusion. Additionally, informed consent to follow-up was obtained if relevant. The study was approved by The Scientific Review Board and Ethical Committee of the study hospital and the Danish Data Protection agency. The present study was not within the jurisdiction of The Danish National Committee on Health Research, Subcommittee on Developing Countries.

2.4. Statistical analyses. Before initiating the study, sample size was calculated. Assuming a mortality risk of 5% and a predictor prevalence of 12%, including 2151 patients would enable us to detect odds ratios (OR) of 2, at significance level = 0.05 with a power = 0.8. Based on previous admission figures, we evaluated the sample size feasible.

Data were entered in Microsoft Access 97 and analyzed in STATA IC 11 (Texas, US). Double entry of a random sample of 10% of the questionnaires showed less than 5% discrepancy.

Proportions were compared using Chi-square. Associations between predictors and outcome was analyzed in multivariate logistic regression using backwards elimination if $p > 0.20$. The analyses were performed for both primary and secondary outcomes. Associations were analyzed in multivariate logistic regression analyses using backwards elimination if $p > 0.20$. The predictors were grouped according to the time they appeared; in socio-demography, pregnancy-delivery, neonatal-history and clinical-admission-condition. Each predictor was adjusted for other predictors within the same group and the predictors in the previous groups. First socio-demography predicators were adjusted within the group. Then pregnancy-delivery predictors were included in the model and adjusted within the group and for the remaining socio-demography predictors. Remaining predictor groups were entered in a similar manner. Gender, birth weight (≤ 1,000, 1,001-1,500, 1,501-2,500 and >2,500g) and admission age (0-1, 2-7 and 8-28 days) were kept throughout the model regardless of p-value. In the model including all groups, all predictors remaining were analyzed repeating backwards elimination, to further reduce the number of predictors in the final model. Possible interactions for gender and birth weight (>/≤ 1,500g) and trend test for rank scale predictors were investigated in the final model. If data on the outcome or predictor was missing, the neonate was excluded from analyses. Hence data imputation was not applied.

The level of significance was set to 5% (2-sided P-value). Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported.

3. Results

3.1 Patients. Overall 5802 neonates were admitted during the study period. Thirty-nine neonates had incomplete data from the central hospital registry and were excluded. In the remaining 5763 neonates (>99%), described separately (A. Kruse, accepted for publication), the in-hospital case fatality rate was 4% (n=235). Another 1% (n=67) had WLST. Males made up 55%, the median admission age was 7 days (interquartile range 2-17 days) and the median length of stay was 7 days (interquartile range 4-15 days). No neonates died or had WLST outside the inclusion wards. Twenty-two neonates were dead at arrival to the hospital.

3. 2 Cohort. Figure 2 shows the flowchart of the neonates included in the cohort. No families declined participation. Of all 5802 neonates admitted, 2493 did not meet the inclusion criteria. The remaining 3309

neonates from the 3 inclusion wards were assessed eligible, of which 1012 were evaluated more than once because of internal transfers. This is also the reason why more than half of the neonates in SICU were included. Hence 2264 neonates were enrolled, of which 2221 completed the questionnaire (missing 43). Due to missing discharge data (n=25), 2196 neonates (38% of all neonates) were available for final analysis.

3.3 Characteristics. The cohort population was characterized by 59% males, significantly more than in the total neonatal hospital population ($p < 0.01$). The premature constituted 33%, 35% of these < 32 gestational weeks. The median birth weight was 2700g (interquartile range 2000-3100, total range 700-5000), median admission age was 2 days (interquartile range 0-8) and median admission duration 13 days (interquartile range 7-23) (data not shown). The distribution of the major diagnoses among the entire cohort and among dead neonates in the cohort is shown in figure 3. To compare, figure 4 shows the global death causes according to The WHO Child Health Epidemiology Reference Group (CHERG) [5].

3.4 Outcome. In the cohort 198 died within the neonatal period, corresponding to a case fatality rate of 9%, significantly more than in the total neonatal hospital population ($p < 0.01$). Another 51 neonates had WLST (2%). It was possible to contact 35 of these families (69%) of which 33 were dead and 2 alive at 28 days of age. Sixteen families, we were not able to follow-up, because the family did not have access to telephone (n=10), wrong telephone number (n=2), or permission to call was not obtained (n=4).

3.5 Predictors. The unadjusted odds ratios for death are shown in the appendix. The adjusted odds ratios for the predictors of death in the final model are shown in table 2. The final model included complete data on 168 deaths among 1901 neonates (unbiased in regards to death compared to the full cohort). None of the socio-demographic predictors were associated to death; hence gender, ethnicity, and parental education were insignificant ($p > 0.20$). Among pregnancy-delivery predictors low birth weight was significantly associated to death as expected ($p < 0.01$); very low birth weight (≤1500 g) OR=2.13 (CI 1.25-3.63) and extreme low birth weight (≤ 1000g) OR=4.34 (CI 1.46-12.96) compared to normal birth weight peers (>2500g). In accordance, trends test (≤ 1000, 1001-1500, 1501-2500 and >2500g) was significant (p=0.03). None of the predictors related to neonatal history remained in the final model. Admission age over 7 days predicted a significantly decreased risk of dying, OR=0.43 (CI 0.25-0.75), as expected. Impaired respiration, circulation and consciousness at admission were significantly associated to death: respiratory failure OR 5.19 (CI 2.89-9.30), shock OR 2.25 (CI 1.17-4.34) and lethargy-coma OR 3.03 (1.95-4.69), $p < 0.03$ When respiratory failure was not present, chest retraction was also associated to death ($p < 0.01$). No interaction was found, when testing for birth weight and gender in the final regression model.

The same analysis was performed for the secondary outcome death or WLST. The main findings were similar.

4. Discussion

In this prospective cohort of more than 2000 Vietnamese neonates, notably gender, ethnicity, and parental education were not associated to neonatal hospital death. Admission after the first week of life was associated with decreased risk of death. Very low birth weight, impaired respiration, circulation and consciousness at admission were associated with increased risk of dying.

In accordance with the inclusion criteria, we attempted to focus on the vulnerable neonates and the case fatality rate was significantly higher in the cohort compared to the entire hospital population. More subtle

inclusion bias, however, cannot be excluded since the selection of neonates in SICU was not done by strict randomization.

Our primary outcome was death. The secondary outcome also included WLST, since these neonates were discharged on manual bagging to die at home. Of the neonates followed-up, the great majority died, but not all. Follow-up, however, was poor. Analysis including the secondary outcome did not change the main findings.

Of the predictors, ethnicity, gender and parental education were not significantly associated to hospital survival once admitted. This may indicate a fair hospital management of infants. It is an important finding, since these socio demographic factors have been shown to be of importance to infant survival in developing countries [2,19-21], though more pronounced in later infancy [22]. However, the socio demographic factors may influence who is admitted to the hospital in the first place. The cohort roughly corresponded to the catchment area in terms of education level and ethnicity [23,24].
Gender was not associated to death. But more males were born in the catchment area, admitted to the hospital and enrolled in the cohort. The unbalanced gender birth ratio of 109.7 male live births /100 female live births is a concern in Vietnam [25], since male preference is known in the region [26-29]. But the male bias in the hospital and cohort may reflect the known vulnerability of male infants [2,19,30-32].

Prematurity is a well established cause of neonatal mortality [2,33], but gestational age was often unknown and not estimated systematically in the hospital. Birth weight was therefore used as proxy. The odds ratios were lower than expected, which may reflect admission bias, since prematurity is likely to be underrepresented in the hospital (A. Kruse, submitted for publication). The neonatal history predictors were chosen because they have been shown to indicate need of referral to hospital in resource-poor settings [6-9]. However, none of those remained in the final model.

The predictors reflecting clinical condition on admission were the most important predictors of neonatal hospital death. It is not surprising that the vital parameters were significantly associated to death. Currently, pediatric early warning scores [34-36] are systematically being implemented in hospitals in developed countries, and may also be a way forward in the present context. The study did not explore the effects of clinical care within the hospital. This complex field was examined in a separate audit study.

ICD10 discharge diagnoses were grouped according to the major causes of neonatal mortality globally. Infection and congenital malformation comprised almost three quarters in both the entire cohort and among the dead neonates. Rough comparison to global distribution of death causes shows striking differences. Asphyxia was the diagnosis group differing most markedly with few admissions and a relatively low risk of death, most likely indicating a strong admission bias against severe asphyxia. These indications point to a selected population in the cohort and presumably in the all the hospital (Kruse A, accepted for publication).

The external validity of our findings depends on the comparability of the populations and hospitals. The referral process to our hospital from the enormous catchment population of more than 700.000 live births is obviously complex. Hence the 150 neonatal beds are far less than the estimated requirement of 2100 neonatal beds for the catchment area (3 per 1000 births) [37]. However, specialized hospitals like the present, exists throughout the developing world and pre-hospital selection of neonatal patients is likely to be a general concern.

5. Conclusion

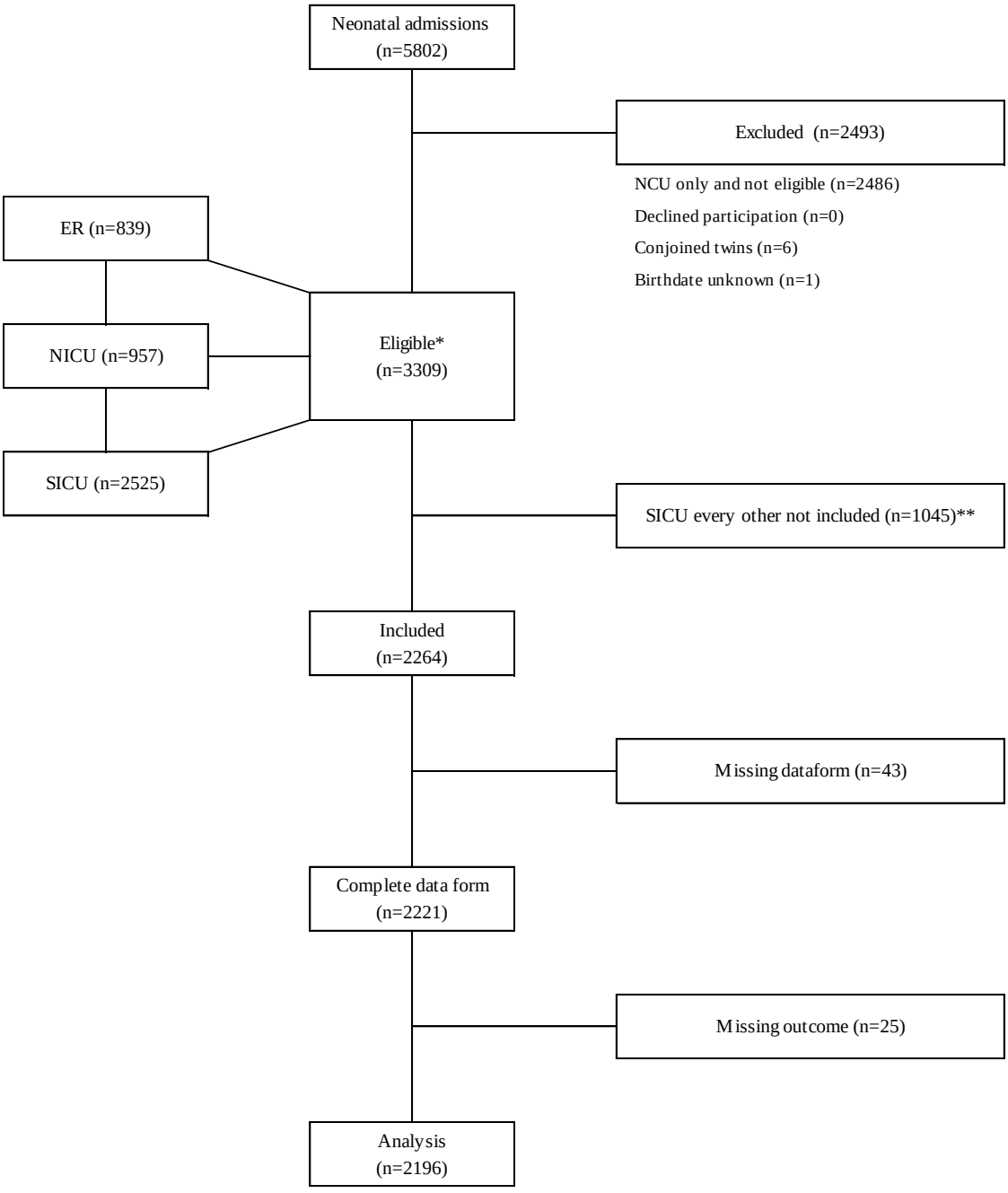
In this prospective cohort study of 2196 neonates in a pediatric hospital in South Vietnam, notably gender, ethnicity and parental education were not associated to hospital death. Clinical admission condition; impaired respiration, circulation and consciousness were associated to death. Thus, our findings support the importance of basic vital parameters to identify neonates in particular need of active early management. Our findings need to be confirmed and the use of early warning scores should be explored to improve neonatal hospital survival.

Acknowledgement

This study is funded by Danida, King Christian the Xth Fund, the Dagmar Marshall Fund and Copenhagen University Faculty of Health Science PhD Travel Fund. We thank the staff at Pediatric Hospital No. 1, Dr Dinh Phuong Hoa, Reproductive Health, Ministry of Health, Hanoi and the Danish Vietnamese Association for their cooperation.

5. Tables and figures

Figure 1 Flowchart of neonates included in the cohort



NCU (Neonatal Care Unit), ER (Emergency Room), NICU (Neonatal Intensive Care Unit), SICU (Neonatal Semi-Intensive Care Unit)

*Because of internal transfers, ward numbers add up to more than the total eligible number

** Because of internal transfers , less than every half of SICU neonates were not included

Table 1 Unadjusted Odds Ratios for predictors of neonatal death (appendix)

Table 2 Final model of adjusted Odds Ratios for predictors of neonatal death

OR (odds ratios), CI (95% confidence intervals)

PREDICTOR	OR (CI)	p
Gender		
Male	1.00	
Female	0.99 (0.68-1.44)	0.97
Birthweigth (gram)		**0.01**
<=1000	4.34 (1.46 - 12.96)	**<0.01**
1001-1500	2.13 (1.25-3.63)	**<0.01**
1501-2500	1.20 (0.78 - 1.84)	0.40
>2500	1.00	
Admission age (days)		**<0.01**
0-1	1.00	
2-7	1.14 (0.71 - 1.81)	0.59
8-28	0.43 (0.25 - 0.75)	**<0.01**
Color sign		**0.01**
Pink	1.00	
Jaundice	1.32 (0.77 - 2.25)	0.30
Cyanosis	2.48 (1.46 - 4.21)	**<0.01**
Pale	2.07 (0.92 - 4.71)	0.08
Consciousness		
Awake	1.00	
Lethargy-unconcious	3.03 (1.95 - 4.69)	**<0.01**
Respiratory Failure*		
No	1.00	
Yes	5.19 (2.89 - 9.30)	**<0.01**
Grunting**		
No	1.00	
Yes	0.65 (0.34-1.24)	0.19
Retraction**		**<0.01**
No	1.00	
Moderate	2.05 (1.29 - 3.25)	**<0.01**
Severe	3.18 (1.63-6.21)	**<0.01**
Shock***		
No	1.00	
Yes	2.25 (1.17-4.34)	**0.02**

*Defined as gasping/prolonged apnea/intubation/bagging

** If no respiratory failure

*** Defined as minimum 2 out of 3
(tachycardia/bradycardia, prolonged capillary refill time, weak pulse)

Figure 3 Distribution of ICD 10 diagnoses

Fig 3a
ICD10 diagnoses among all neonates in the cohort (n=2196)

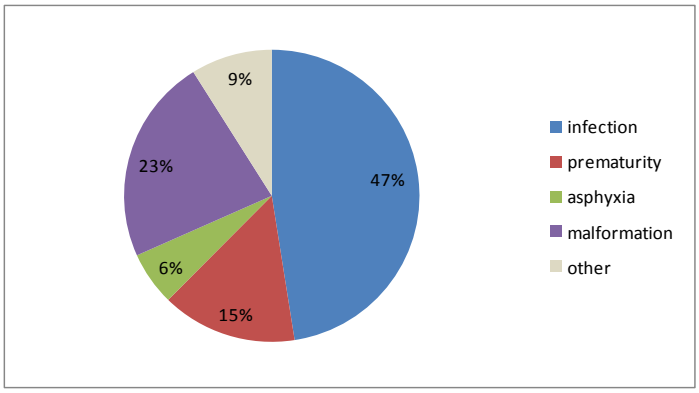


Fig 3b
ICD10 diagnoses among dead neonates in the cohort (n=198)

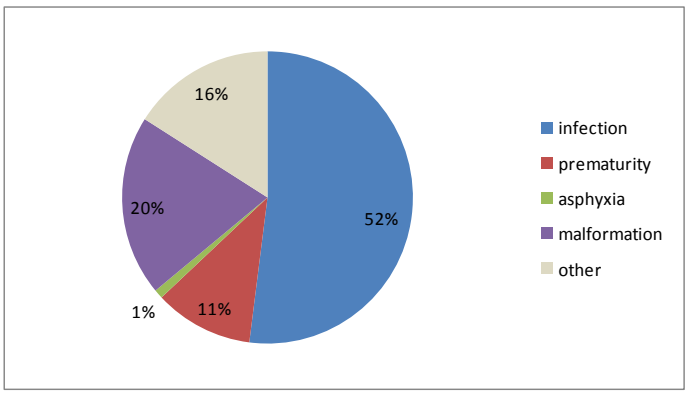
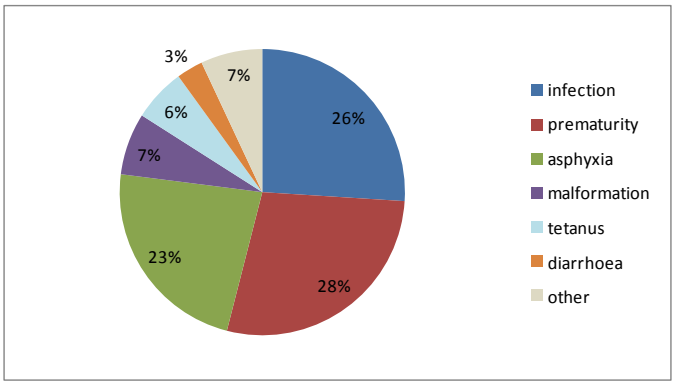


Figure 4 Distribution of global death causes



According to CHERG, Child Health Epidemiology Reference Group [5]

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APPENDIX 3

Original paper III

Neonatal Blood Stream Infections in a Pediatric Hospital in Vietnam: a Cohort Study

by Alexandra Yasmin Kruse[1], Do Huu Thieu Chuong[2], Cam Ngoc Phuong[2], Than Duc[3], Lone Graff Stensballe[4], Jorgen Prag[5], Jorgen Kurtzhals[6], Gorm Greisen[7, 8]
and Freddy Karup Pedersen[1, 4, 8]

[1]*International Child Health Research Unit, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark*
[2]*Neonatal Intensive Care Unit, Paediatric Hospital no 1, Ho Chi Minh City, Vietnam*
[3]*Department of Clinical Microbiology, Paediatric Hospital no 1, Ho Chi Minh City, Vietnam*
[4]*Department of Paediatrics and Adolescent Medicine, JMC, Rigshospitalet - Copenhagen University Hospital, Copenhagen, Denmark*
[5]*Department of Clinical Microbiology, Viborg Hospital, Viborg, Denmark*
[6]*Centre for Medical Parasitology, Department of Clinical Microbiology, Rigshospitalet – Copenhagen University Hospital and Department of International Health, Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark*
[7] *Department of Neonatology, JMC, Rigshospitalet – Copenhagen University Hospital, Denmark*
[8]*Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark*

Correspondence: Alexandra Y Kruse, International Child Health Research Unit, 4072, Juliane Marie Center, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark,
Tel: +45 35453864, email: alexandra.kruse@dadlnet.dk

Summary
Septicemia and blood stream infections (BSI) are major causes of neonatal morbidity and mortality in developing countries. We prospectively recorded all positive blood cultures (BSI) among neonates admitted consecutively to a tertiary pediatric hospital in Vietnam during a 12-months period. Among 5763 neonates 2202 blood cultures were performed, of which 399 were positive in 385 neonates. Among these 64 died, 62 in relation to septicemia. Of the BSI isolates, 56% was known pathogenic and 48% was Gram-negative bacteria, most frequently *Klebsiella* spp. (n=78), *Acinetobacter* spp. (n=58) and *Escherichia coli* (n=21). Only 3 *Streptococcus* spp. were identified, none group B. Resistance against antibiotics applied was common. The mortality was highest in neonates with Gram-negative BSI compared to no isolates and Gram-positive bacteria. ($p < 0.01$). In this setting, the majority of BSI were likely to have been transmitted from the environment. Improvement of hygienic precautions and systematic BSI surveillance is recommended.

Key words: bacteremia, blood culture, developing country, lower income country, neonate, newborn, sepsis, septicemia, Vietnam

Introduction
Globally, infections cause more than a third of the deaths among neonates (≤ 28 days of age), the vast majority in the developing countries [1-4].

Septicaemia is among the most severe infections usually defined by a positive blood culture (blood stream infections, BSI) and systemic clinical signs [4-7]. In the absence of consensus of specified diagnostic criteria, blood culture is considered the gold standard to establish the diagnosis [7]. Since septicaemia is difficult to diagnose on presentation and may develop rapidly, prompt empirical treatment is prescribed and later adjusted according to blood culture result and clinical response.

The aetiology of BSI vary in time and place. Compared to high-income countries, neonatal septicaemia in lower-income countries is more frequent, more commonly caused by Gram-negative bacteria and mortality higher. Furthermore, antibiotic resistance is an increasing problem [8-14]. Vietnam has risen from one of the poorest countries in the world to a lower middle-income country with almost 90% of women delivering in health care facilities [9]. To our knowledge no peer-reviewed studies are available on neonatal septicaemia or BSI in Vietnam and few are published from the region [13, 15, 16].

Our aim was to investigate the incidence and characterize the pattern of neonatal BSI in a tertiary hospital in Vietnam. We investigated the incidence, distribution and susceptibility of microbial species. Furthermore, we examined the septicaemia related mortality among neonates with BSI and the association to isolate group.

The study was approved by The Scientific Review Board and Ethical Committee of the study hospital and The Danish Data Protection Agency. The study is not within the jurisdiction of The Danish National Committee on Health Research Ethics, Subcommittee on Developing Countries.

Patients and Methods
Setting
The study was conducted at The Paediatric Hospital Number 1 (PH1) in Ho Chi Minh City. It provides pediatric care only and is a tertiary referral hospital for South Vietnam, in 2009 comprising 726,578 live

births corresponding to half of the deliveries in the country [17]. In PH1, approximately 95% of patients are referred from other health care facilities, 2/3 from the provinces and 1/3 from the city. The 150-bed neonatal department offered the most specialized care in the country.

Participants and data collection

During the 12-months study period from February 2009 – February 2010, a prospective cohort was established of all neonates (≤ 28 days of age) admitted to PH1. Basic demographic and clinical data were obtained from the central hospital registry, including data on gender, birth date, admission period, discharge diagnoses using The International Classification of Diseases version 10 (ICD 10) [18] and discharge outcome. To ensure correct registration of deaths, cases of confirmed neonatal death were also listed separately by the project group throughout the study period according to clinical staff, ward books, ward meetings and daily hospital conferences.

The indication for blood culture was severe clinical signs of septicemia, often supported by other paraclinical results. Culture was performed prophylactic only in the few cases of exchange transfusion. Results of neonatal blood cultures were collected from the registration book and electronic database in The Department of Microbiology. When a culture was positive, sampling date, isolate and antibiotic susceptibility pattern were registered.

Laboratory methods

A peripheral blood sample of 1-2 ml was drawn into a pediatric blood culture bottle (BACTEC, Becton Dickinson, New Jersey, US) after skin disinfection with povidone-iodine and alcohol. Bacterial growth was detected automatically (BACTEC 9240/9050 reader). Blood culture bottles were incubated for 6 days. If negative, a one-day subculture confirmation was carried out. If positive, cultures were examined by microscopy of Gram-stained smears and cultured on 5% sheep blood agar and MacConkey at 35°C moist air. If fungal infection was suspected, Sabouraud agar was included. The agar plates were manufactured at the laboratory of PH1 from purchased ingredients (Becton Dickinson). Bacterial isolates were identified by conventional methods [19] using commercially available media (Bio Rad, Philadelphia, US). According to Gram-stain, antibiotic susceptibility of pathogens was tested on Mueller Hinton Agar (Becton Dickson) using disc diffusion (Oxoid, Hampshire, UK) for relevant antibiotics [20].

Data analysis

Data were analyzed in STATA IC 11 (Texas, US). Each death among neonates with BSI was audited to determine whether it was a septicemia-related-neonatal-death. This was defined as septicemia assigned as either direct or underlying death cause according to the classification of ICD 10. The audit group included experienced neonatologists and pediatricians from PH1 and Righospitalet (Denmark). To test the association between grouped isolates and septicemia-related-neonatal-death, Chi-squared test was performed (2-sided p-value set to 5%).

Results

Patients

In the study period, 5802 neonates were admitted to the hospital. Thirty-nine neonates, none with BSI, were excluded due to lack of basic data (< 1%). The remaining 5763 neonates constituted the cohort previously described (A. Kruse, accepted for publication), of which 34% were admitted age 0-3 days and 62% were diagnosed with infection. Overall neonatal case fatality rate was 4%.

Blood Stream Infections
In the cohort, 2202 neonates had blood cultures performed, of which 399 samples in 385 neonates were positive. Fourteen neonates had 2 positive cultures performed with different isolates at different times (> 3 days apart). BSI was verified in 1.3/1000 admission days.

The characteristics of neonates with BSI are shown in table 1. The majority had late onset BSI (> 3 days of age) (84%) and infection as discharge diagnosis (64%). Sixty-four neonates (17%) died. Another 5 neonates had life-sustaining-treatment-withdrawn because of poor prognosis and were discharged alive on manual bagging to die at home.

Isolates
The distribution of isolates is shown in table 2. Several of the species were not specified. Of the BSI, 56% were caused by isolates considered known pathogenic. The remaining isolates, all coagulase negative *Staphylococcus* (CoNS), were considered potentially pathogenic in neonates. Among the pathogenic isolates, 86% were Gram-negative bacteria, *Klebsiella* spp., *Acinetobacter* spp., *Escherichia coli* and *Enterobacter* spp. being the most frequent isolates recovered. Streptococci were isolated in only 3 neonates and were alpha-hemolytic.

Mortality
Sixty-four neonatal deaths occurred among the neonates with BSI, 62 (97%) were classified as septicemia-related-neonatal-deaths corresponding to a case fatality rate of 16% (62/385). Table 3 shows their characteristics. The mortality was significantly higher among neonates with confirmed BSI and the risk varied by group of isolates, table 4 ($p < 0.01$). CoNS seemed of clinical interest compared to those without confirmed BSI. As expected, the mortality risk was significantly higher among neonates with Gram-negative BSI.

Susceptibility to antibiotics
Table 5 shows the antibiotic susceptibility patterns of the isolates. Decreased antibiotic susceptibility was common, including resistance towards antibiotics used empirically in the hospital. Hence, resistance towards both first line (ampicillin, gentamycin and cefotaxime) and second line (other cephalosporins and quinolones) treatments was substantial among the Gram-negative bacteria. Susceptibility was retained for the broad spectrum carbapenemes used as third line therapy, although *Acinetobacter* spp. showed emerging resistance (43%). Among *Staphylococcus* aureus, methicillin (oxacillin) resistant accounted for 45%. No vancomycin resistance was found among the Gram-positive bacteria.

Discussion
BSI was diagnosed in almost one fifth of blood cultures performed in this neonatal hospital cohort. In contrast to the high proportion of Gram-negative isolates *Streptococci* spp. were rare resembling the pattern reported in other resource limited settings [8-13, 15].

The study population was not representative of the huge catchment population of live births delivered outside the hospital. The population was selected, since the vast majority was referred to this tertiary hospital from other health care facilities. Although more severe cases would be expected in this setting, not all severe cases are likely to have been referred. Early onset BSI were probably underrepresented, as the majority of neonates were more than 3 days old at admission. Some neonates are likely to have died before or been evaluated too

severely ill for referral, because transport is often long and the equipment basic. Further, the staff or family may have regarded the prognosis too poor to justify the direct and indirect expenses involved in referral to higher level of care.

We studied BSI as a surrogate for septicaemia, since only limited clinical data were accessible and no data on other paraclinical support were obtained. We assumed neonates with BSI to have septicemia signs, since it was the main indication for blood culture. Further, we expected infection diagnosis to be a rough indicator of clinically relevant infections. However, the relation between BSI and infection discharge diagnosis was poor. Several explanations for this are possible. Infection diagnosis might not have been assigned, when other diagnoses were relevant and infection diagnoses also included localised infections.

The predominance of *Klebsiella* spp., *Acinetobacter* spp. and *Escherichia coli* is in accordance with other hospital studies in developing countries [8-13, 15]. *Acinetobacter* spp. was less pathogenic than the other Gram-negative bacteria identified in the study, but still a significant cause of death. Due to emergence of multi-resistance [21-23], this species may play an increasing role in septicemia related mortality. The majority of BSI was late onset and likely to have been externally transmitted from the environment via care providers, including nosocomial infections acquired at PH1 or at the previous health care facility. However, misclassification of onset is possible, since BSI might have been present earlier than diagnosed. Standard blood culture at admission during a surveillance period could help to locate the source. Nosocomial transmission is well known for the majority of the isolates identified [11-13] and hygienic precautions are of major importance to prevent BSI.

The importance of CoNS in neonatal septicemia has been disputed. Our findings suggest they may be of clinical relevance, although few neonates had central vascular catheters, which are associated with CoNS colonisation of pathogenic importance [7, 8, 12, 24]. Only 3 streptococci were recovered, none beta-hemolytic. *Streptococcus* group B is a leading cause of neonatal septicemia in high-income countries, but less frequently reported in lower income countries and especially in South East Asia. However, the burden in developing countries is unclear [13, 25-30].

The overall mortality was significantly higher among neonates with BSI as expected and within the range shown by others in resource poor settings [8, 15, 31]. We classified 97% of deaths among neonates with BSI as septicemia-related neonatal deaths according to ICD10 classification. However, in most deaths more causes were present. Congenital malformation, prematurity (gestational age < 33 / low birth weight < 1800g) and asphyxia are other major causes of neonatal mortality globally [1]. These conditions were present in 40-60% of septicemia-related-neonatal-deaths in the isolate groups compared. It should also be kept in mind that severely ill neonates are at high risk of infection and prone to have blood culture performed, hence it is difficult to determine whether BSI is the cause or the consequence of severe illness.

Antibiotic treatment at the time of sampling was not reported. Resistance against the first lines of antibiotics applied in the hospital was a common problem. Increasing antibiotic resistance, especially among Gram-negative bacteria, is a major concern in developing countries [8, 10-12, 32-35]. The use of antibiotics in- and outside health care facilities and in farming is a likely cause [34, 36]. Carbapenems could be considered as the first choice for Gram-negative BSI with severe clinical signs of septicemia [37] in this setting, but meropenem-resistant *Acinetobacter* spp. should be monitored very carefully. Future alternatives to initiate effective antibiotics in emerging economy countries like Vietnam could be to target antibiotics fast by

identification of isolated bacteria using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) [38, 39] or hybridization techniques [40, 41].

Among Gram-positive bacteria, vancomycin susceptibility was preserved. Almost half of *Staphylococcus* aureus isolates were meticillin resistant (MRSA), but numbers were too small to allow any firm conclusions.

Conclusion

Among all 2202 blood cultures, 399 BSI were verified among 385 neonates. The majority was late onset and caused by known pathogenic species. Gram-negative bacteria comprised the vast majority of these, of which *Klebsiella* spp., *Acinetobacter* spp. and *Escherichia* coli were the most frequent. None *Streptococcus* group B were identified. The septicemia related mortality was highest among neonates with Gram-negative BSI. Resistance towards antibiotics applied in the hospital was common and carbapenems could be considered first choice for Gram-negative BSI with severe clinical signs. Improvement of hygienic precautions and implementation of BSI surveillance is recommended to decrease septicemia morbidity and mortality among neonates in Vietnam.

Acknowledgement

The authors acknowledge the support from the study hospital PH1.

Funding

This work was supported by The Danish International Development Agency (DANIDA).

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Tables

TABLE 1

Characteristics of neonates with BSI (n = 385)*

Variables	n (%)
Gender	
Male	152 (40)
Female	233 (60)
Admission age (days)	
≤ 1	101 (26)
2 to 3	57 (15)
4 to 28	227 (59)
Central vascular catheters (at time of sampling)	10 (3)
Onset (≤ / > 3 days of age at sampling)	
Early	60 (16)
Late	325 (84)
Dischage diagnoses	
Infection	249 (64)
Sepsis	84
Menigitis	10
Pneumonia	70
Gastrointestinal	45
Other	40
Prematurity	24 (6)
Asphyxia	6 (2)
Congenital malformation	52 (14)
Other	54 (14)
Neonatal outcome (28 days of age)	
Discharged	171 (45)
Admitted	145 (38)
Dead	64 (17)
Life-sustaining-treatement withdrawn	5 (1)

*BSI: blood stream infections

TABLE 2

Distribution of BSI isolates (n=399)*

in 385 neonates, 14 duplet culture samples with different isolates at different times

Pathogenicity	Isolate	(n)
Known	*Klebsiella* spp	78
	Acinetobacter spp	58
	Escherichia coli	21
	Enterobacter spp	16
	Morganella spp	8
	Pseudomonas spp	6
	Proteus spp	3
	Burkholderia spp	2
	Staphylococcus aureus	11
	Enterococcus spp	5
	Streptococus spp (alph-hemolytic)	3
	Candida spp	13
Potential	coagulase negative *Staphylococcus*	175
Total		399

*BSI: blood stream infections

TABLE 3

Characteristics of septicemia related deaths among BSI (n=62)*

Variable	n
Isolate	
Klebsiella spp	19
Acinetobacter spp	10
Escherichia coli	5
Enterobacter spp	5
Morganella spp	2
Pseudomonas spp	1
Streptococus spp	1
Staphylococcus aureus	2
Enterococus spp	1
Candida spp	3
Staphylococcus coaulase negative	13
Admission age (days)	
≤ 1	23
2 - 3	18
4 - 28	21
Onset (≤ / > 3 days of age at sampling)	
Early	17
Late	45
Diagnosis	
Infection	34
Preterm	10
Malformation	5
Asphyxia	3
Other	10

*BSI: blood stream infections

TABLE 4

Association of septicemia related mortality and isolate

Isolate	OR	CI
No confirmed Blood Stream infection	1.00	
Staphylococcus coagulase negative	1.54	0.84-2.83
Acinetobacter spp	3.95	1.93-8.09
Other Gram-negative baceteria	6.26	3.96-9.89

$p < 0.001$

Table 5
Bacteriae susceptibility pattern in 399 BSI (Blood Stream Infections) and empiric antibiotics recommendation in the hospital

(% (sens/total cultured))

Antibiotics and indication	Gram-negative species						Gram-positive species			
	Kleb (n=78)	Acinetob (n=58)	E Coli (n=21)	Enterob (n=16)	Morg (n=8)	Pseudo (n=6)	CoNS (n=175)	SA (n=11)	Enteroc (n=5)	Strep (n=3)
1 line										
Ampicillin	0	15	14	7	13	0				
Cefotaxime	14	18	42	38	48	17				
Gentamicin	15	50	43	38	25	52	34	72	0	0
2. line										
Ceftazidime	29	29	58	50	50	67				
Ciprofloxacin	29	78	52	38	25	67				
Pefloxacin	12	73	52	44	14	17	37	86	0	0
2-3. line										
Vancomycin							99	100	100	100
Cefepime	19	42	40	47	43	67				
Timentine*	18	41	48	38	29	67				
3. line										
Meropenem	98	57	100	100	100	100				
Imipenem	96	59	100	88	100	83				
SA suspicion										
Oxacillin							16	45	0	67
Rifampicin							84	100	60	100

*Timentine = ticarcillin/klavulanova acid

Kleb (*Klebsiella* spp), Acb (*Acinetobacter* spp), Enterob (*Enterobacter* spp), Morg (*Morgenella* spp), Psudo (*Pseudomonas* spp), CoNS (coagulase negative *Staphylococus*), SA (*Staphylococus* aureus), Enteroc (*Enterococus* spp), Strep (*Streptococus* alpha hemolytic)

APPENDIX 4

Original paper IV

Prospective Audit Study of

Neonatal Deaths in a Paediatric Hospital in Vietnam

Alexandra Y. Kruse[1], Cam N. Phuong[2], Binh T. T. Ho[2], Lone G. Stensballe[3], Freddy K. Pedersen[1, 3, 4] and Gorm Greisen[4, 5]

[1]International Child Health Research Unit, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark
[2]Neonatal Intensive Care Unit, Paediatric Hospital 1, Ho Chi Minh City, Vietnam
[3]The Department of Paediatrics and Adolescent Medicine, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark
[4] The Faculty of Health and Medical Science, Copenhagen University, Copenhagen, Denmark
[5]Department of Neonatology, JMC, Rigshospitalet – Copenhagen University Hospital, Copenhagen, Denmark

Correspondence: Alexandra Y Kruse, International Child Health Research Unit, 4072, Juliane Marie Centre, Rigshospitalet – Copenhagen University Hospital, 2100 Copenhagen Ø, Denmark, Tel: +45 35453864, email: alexandra.kruse@dadlnet.dk

ABSTRACT

Background

Neonatal mortality (≤ 28 days) comprises more than half of child mortality in Vietnam. Although the vast majority is presumed to die in health care facilities, there is a paucity of neonatal hospital mortality data. Audit is an established analysis to investigate risk factors of death in healthcare management.

Objective

In a structured neonatal mortality audit, we assigned cause and potentially avoidable risk factors in a consecutive series of hospital deaths in Vietnam.

Methods

Among all neonates admitted to a tertiary paediatric hospital in a 12 month period 2009 – 2010, we prospectively included neonates who died or were discharged to die at home after withdrawal-of- life-sustaining-treatment (WLST). Eligible neonates were enrolled from the central hospital registry, supplemented by case neonates identified by clinical staff, in ward books and at daily conferences. We attempted to follow-up cases of WLST regarding outcome at age 28 days. The medical file of each case neonate was reviewed in a structured audit classifying: chance of survival and normal development at arrival, discharge outcome, cause of death/expected death according to two classification systems (International Classification of Diseases 10th revision and Child Health Epidemiology Reference Group), and potentially avoidable risk factors of death during the hospital stay.

Results

Among all 5763 neonates admitted, 302 case neonates were included; 235 died in hospital and another 67 had WLST. At follow-up 38 WLST cases were dead and 2 were alive. In the remaining 27 cases follow-up was not possible. According to both classification systems, the major causes of death/expected death were congenital malformations, prematurity and severe infections. We identified 6 potentially avoidable risk factors, of which one or more was present among 85% (60/71) of the neonates with a relatively good prognosis at arrival. The risk factors were: delayed recognition and/or response to danger signs, suboptimal internal transfers, nosocomial infections, suboptimal septicaemia management, shortage of available equipment, and family and/or medical staff misperception of prognosis.

Conclusion

Among 302 neonates who died or were discharged after withdrawal-of-life-sustaining-treatment to die at home, the major causes were congenital malformations, prematurity and severe infections. Among the neonates with relatively good prognosis at arrival, we identified 6 potentially avoidable risk factors, which could be addressed without implementation of new technologies or major organizational changes.

KEY WORDS

Audit, avoidable risk factors, developing country, end-of-life-decision, hospital, lower income country, modifiable risk factors, mortality, neonate, newborn, Vietnam, withdrawal-of-life- sustaining-treatment

ABBREVIATIONS

CHERG: Child Health Epidemiology Reference Group hierarchical classification of neonatal mortality
ICD10: The International Classification of Diseases 10th revision
PH1: Paediatric Hospital no 1
WLST: Withdrawal-of-life-sustaining-treatment
(and discharged alive on manual bagging to die at home)

INTRODUCTION

Neonatal mortality remains an important global child health issue. Among the millions of children dying annually (before the age of 5 years), the vast majority die in developing countries and neonates (≤ 28 days of age) constitute more than 40%. However, the reduction in neonatal mortality lags behind and hampers the fulfillment of The Millennium Development Goal to reduce child mortality [1].

Vietnam is a developing country with emerging economy, where almost 90% of women deliver in health care facilities [2,3] and presumably remain in hospital the first days after birth. This is the most vulnerable time in the neonatal period [4] and therefore, the majority of neonatal deaths are presumed to occur in hospital.

To our knowledge no peer-reviewed reports on neonatal hospital mortality is available from Vietnam. We chose the qualitative audit method to describe and explore the sensitive issue of the complex management preceding neonatal death in a specialized hospital. Audit is a well established method to investigate hospital mortality neutrally in a no-blame atmosphere in order to improve care by collecting data, identifying avoidable risk factors, synthesizing and implementing recommendations [5-9]. Audit has particularly been applied to study perinatal mortality [10-14]. Studies including the entire neonatal period have been conducted in other resource limited settings [15-18]. Whether implementation of audit can reduce mortality has been disputed [6,7,19].

The aim of the present study was to perform structured audits of all neonatal deaths in a tertiary paediatric hospital in Vietnam in order to:

- Calculate the neonatal case fatality rate
- Determine the cause of deaths
- Identify neonates with a relatively good prognosis at arrival
- Identify potentially avoidable risk factors during the hospital stay

In the group of deaths, we chose to include neonates discharged alive to die at home after withdrawal-of-life-sustaining-treatment (WLST).

PATIENTS AND METHODS

Setting

The study was conducted at The Paediatric Hospital Number 1 (PH1) in Ho Chi Minh City. This tertiary referral hospital for South Vietnam provides paediatric care only. The potential catchment area in 2009 was 726,578 live births corresponding to half of the deliveries in the country [8]. In PH1, approximately 95% of patients were referred from other health care facilities, 2/3 from the provinces and 1/3 from the city. The 150-bed neonatal department offered the most specialized care in the country including mechanical ventilation and surgery, with a bed-occupancy of 154% in the study period.

Patients and data collection

During the 12-months study period from February 2009 – February 2010, a prospective cohort was established of all neonates (≤ 28 days of age) admitted to PH1. Outcome at discharge was obtained from the central hospital registry and all cases of neonatal death and WLST were listed. WLST defined neonates discharged alive on manual bagging (by the family) to die at home. To ensure all eligible neonates were enrolled, we separately listed case neonates according to medical staff, ward books, ward meetings and daily hospital conferences throughout the study period. Medical files of all potential cases were checked to decide

whether the neonate was eligible. Cases of WLST were followed-up by telephone regarding outcome at 28 days of age.

Neonates dead on arrival to the hospital were registered separately.

Audit procedure and data analysis

All case neonates were audited in a structured procedure by an audit group, comprising two experienced Vietnamese neonatologists from the study hospital, a Danish paediatrician and a Danish professor in neonatology. The medical files were reviewed by a Vietnamese group member and English narratives prepared with in-depth descriptions of relevant time-related events. At weekly meetings, each narrative and medical file was audited and a structured report completed. Initially all the group met at internet and face to face meetings. The purpose was to get to know each other as well as the context and to train the concept of audit as a shared open-minded no-shame no-blame process of investigating the course of events in the particular case. It was a dynamic process and any disagreements were discussed and consensus sought. Later the audit meetings were conducted daily in the study hospital by the Vietnamese neonatologists and the Danish paediatrician. Subsequently, the audit report was commented by the Danish professor. Finally, the report was re-evaluated by the rest of the group at audit meetings, deciding if any adjustments should be made to the final report.

The audit comprised the following analyses:

Prognosis at arrival

The Vietnamese audit group members categorized the prognosis at arrival based on chance of survival (>50% / ≤ 50% / unknown) and chance of normal development in terms of growth, psychomotor development and general health (>50% / ≤ 50% / unknown). A relatively good prognosis was defined as chance of both survival and normal development >50%. If either categories were ≤ 50% / unknown, the prognosis was defined as relatively poor

Outcome at discharge

For neonates discharged ≤ 28 days, outcome when leaving the hospital was assigned; dead or WLST. If WLST < 28 days of age, follow-up by telephone was attempted to assign outcome at age 28 days (dead/alive/unknown).

Cause of death

The cause of death/expected death was assigned according to two classifications systems.

The direct and the underlying causes were classified according to The International Classification of Diseases 10th revision (ICD10). The major cause was classified according to Child Health Epidemiology Reference Group hierarchical classification (CHERG). From the top it ranks: major congenital malformation, tetanus, prematurity (gestational age < 33 weeks or birth weight < 1800 g), asphyxia, severe infections, diarrhea and other [20]. This classification was developed to derive global mortality estimates using information from various sources, including verbal autopsies. Therefore it incorporates diagnosis reliability into the hierarchical classification and leaves less room to interpret and prioritize the order of events leading to death. This is different from the refined ICD10 diagnoses usually applied in hospital settings.

Potentially avoidable risk factors

Risk factors were defined as: potentially avoidable within the existing context of the hospital at the time of the study without implementation of new technologies or major organizational changes. Furthermore, the

neonate would, more likely than not, survive the neonatal period (> 50% chance), if this risk factor was not present.

The audit procedures and report forms were pilot tested and adjusted before the study period. Data were entered in EpiData 3.1 (EpiData Association, Odense, Denmark). The audit procedure was performed twice in a random sample of 10% of the cases and when compared less than 5% discrepancy was revealed. Data entry discrepancy was less than 5% in a random sample of 10% of the reports entered doubled. To test for associations Chi^2 test was performed (2-sided p-value set to 5%).

ETHICS

Informed consent was obtained from the family before enrollment. If relevant, separate follow–up permission was obtained. The study was approved by The Scientific Review Board and Ethical Committee of the study hospital and The Danish Data Protection Agency. The study was not within the jurisdiction of The Danish National Committee on Health Research, Subcommittee on Developing Countries.

RESULTS

Patients

Of the 5802 neonates admitted to the hospital during the study period, 302 (5%) neonates died or had WLST. All were included in the study. Another 22 neonates were dead on arrival to the hospital and were not included. Among the case neonates, less than 20% were ≤ 1500g (table 1). Of the 171 case neonates with known gestational age, 32% was < 32 weeks. The majority was male (60%), admitted within day 0 - 1 of life (55%) from a health care facility (96%), and outside Ho Chi Minh City (86%). More than a third died within 24 hours of admission and 6% within 6 hours. Compared to the total neonatal population in the hospital, the male proportion did not differ significantly (p=0.12), but more were admitted in the first day of life (p < 0.01), in accordance with the first days being the most vulnerable [4].

The outcome at discharge was in-hospital death in 235 (78%) and WLST in 67 of the case neonates. Hence neonatal case fatality rate in the hospital was 4%, 5% when including WLST. Among the 40 WLST case neonates in whom follow-up was possible, death was confirmed in the vast majority (n=38). Interestingly, but not significant for the present analysis, 2 infants were alive at 28 days of age. Follow-up was not possible in 27 cases, because the family did not have access to telephone (n=15), permission to call was not obtained (n=10) or the telephone number noted was wrong (n=2).

Cause of death

Cause of death, confirmed or expected, was analyzed for the 302 case neonates included. Figure 1 shows the distribution of causes according to ICD10 classification, the direct cause as well as the underlying cause. Furthermore, the distribution of major death causes according to CHERG classification is shown and compared to global estimates [20]. In all classifications, the three major conditions causing 80% or more of the deaths in the hospital were major congenital malformation, prematurity and severe infections (meningitis, sepsis, pneumonia and peritonitis). However, the proportions differed between the two ICD10 classifications. Compared to underlying cause, severe infection was more frequent as direct cause, whereas prematurity and major congenital malformations were less frequent.

Potentially avoidable risk factors of death

At arrival to the hospital, 71 case neonates were categorized as having a relatively good prognosis in terms of survival normal development (>50%). Among this group, 6 risk factors were identified, of which at least one was present in 60 (85%) of the neonates. In 42% of case neonates recognition and/or response to danger signs were delayed. Internal transfers were suboptimal in 37%. Sepsis related risk factors - nosocomial infections (> 48 hours admission) and suboptimal septicemia management, were present in more than a quarter. Family and/or medical staff misperceptions of prognosis interfered with full treatment in more than a third. In 17% there was a shortage of standard equipment in the hospital.

DISCUSSION

In this setting, among 302 case neonates the major causes of death/expected death were major congenital malformations, severe infections and prematurity according to both ICD10 and CHERG classifications. Six potentially avoidable risk factors were identified among neonates with a relatively good prognosis at admission.

WLST was included in this mortality audit, since discharge on manual bagging carry a very high risk of dying. The prognosis was considered too poor to continue life-sustaining-treatment, but the neonate did not die immediately and was discharged to die at home according to the wishes of the family. At follow-up, however, 2/40 neonates had survived. For another 27 neonates outcome was unknown (follow-up not possible). The audit group accepted this uncertainty. In other contexts, depending on cultural perceptions and resources, this group of neonates might have been kept in hospital, with or without limited treatment.

End-of-life decision is a well described dilemma in neonatal care, not only in developing countries, implying difficult ethical and legal considerations [21-27]. In clinical practice, there is a continuum of care from initiating full treatment to withdrawing all treatment in neonates, who can live for some time or die instantaneously. Euthanasia is not practiced in neonatal care in Vietnam. The process of these decisions are not transparently guided, taken or documented in the study hospital, as these decisions are in some other settings [26,28,29].

We conducted a structured audit to analyze cause of death and the complex process of hospital management using the national [30] and hospital guidelines [30-32] as broad references, when possible. The process relied on consensus within the group and on our ability to share sensitive matters openly in a constructive atmosphere. Nurses would have been relevant to include, but because of language barrier they did not participate. Furthermore, nursing charts included relatively few details, making it difficult to audit the nursing care. Therefore, the present analysis may underestimate the significance of risk factors related to nursing. This is a common weakness of neonatal audits. It is important because the quality of nursing is of crucial in neonatal intensive care.

Major congenital malformations, severe infections and prematurity were the main causes of death/expected death in the classifications of ICD10 as well as CHERG. In ICD10, infection was the most frequent direct cause, whereas congenital malformations and prematurity were the most frequent underlying causes. This is not surprising, since infection potentially is a deadly complication in otherwise non-lethal congenital malformation or viable premature neonates. We applied the CHERG classification to compare to global estimates of the 4 million annual neonatal deaths. This classification was developed as a public health tool,

since information of cause is incomplete or lacking, due to inadequate vital registration system in 98% of the world´s neonatal deaths [20]. Comparing causes in the hospital to global estimates, the proportion of malformations were much higher. This was expected as this tertiary hospital provides neonatal surgery. In contrast, the proportions of asphyxia and prematurity were less, although specialized and intensive care may also be required for these groups. We have previously shown these groups to be underrepresented in the hospital, reflecting a hospital population which is likely to be selected for reasons not only medical [33]. Tetanus and diarrhea did not cause any deaths in the study hospital. In the study, unknown death cause was included, which was not a separate category in the global estimates.

We identified potentially avoidable risk factors of direct importance for neonatal survival. Neonates with a relatively good prognosis on arrival were in focus, since the hospital usually can save and wants to save this group. Only 71 of the total number of 302 case neonates were categorized as having a chance of survival and normal development of more than 50% at arrival given the best available treatment and care in the hospital. This indicates the severity of the case load in the hospital as well as our conservative criteria for this group. We found this important, since the relevance of the risk factors in this population is difficult to question. Accordingly, we focused on risk factors, which required neither investment in new technologies nor major organizational changes. Six risk factors were identified, of which at least one was relevant to 85% in this group of neonates. Risk factors could be interrelated, for example shortage of monitors of saturation and heart rate could influence delay in recognition of danger signs.

In almost half of the group, recognition and/or response to danger signs were delayed, e.g. neonates found in terminal apnea or shock. Severe infections were common. Problems identified were nosocomial infections (diagnosed after 48 hours admission to the hospital) and suboptimal septicemia management including less aggressive antibiotic treatment or insufficient volume in the presence of shock. Suboptimal internal transfers and shortage of available equipment like monitors, airway devices and ventilators were other problems identified in this resource limited setting.

Although this subgroup of neonates were categorized as having a relatively good prognosis at arrival by the audit group, in more than a third of the cases the family and sometimes the medical staff perceived the prognosis too poor and the level of active management was restricted. This may reflect misperception of the prognosis. However, the threshold of acceptable prognosis may vary in different contexts. It is difficult to uncover if the decision was taken on right or wrong premises, taken the rights and needs of the neonate, the family, the hospital and the society into account in this resource limited setting. It has previously been shown that complex socio-economic factors of the neonate and other stakeholders influence the treatment level in resource scarce settings [34].

In 3 cases, the financial situation of the family and hence the ability to care for the neonate was stated as the direct reason. Even though health care for children under 5 years of age is free in Vietnam, hidden user fees and informal incentives exist. Free care does not include outpatient care. Furthermore, the predicted future expenses for the family are of importance, since the public support to children with special needs is very limited. Poverty is a known underlying cause of neonatal deaths [4].

We recognize the special character of the misperception risk factor. Leaving it out of the analyses, the other 5 risk factors identified were relevant to 70% (54/71) of the neonates with relatively good prognosis at arrival.

To complete the audit cycle and address these 6 risk factors, we suggest establishing a working group to investigate possible interventions in the hospital including how to handle perception of prognosis and limiting available treatment, hygienic precautions, scenario training, equipment indications and improved procedures for internal transfer. We did not investigate whether our findings are applicable in other hospital settings. However, similar paediatric hospitals are present in Vietnam and other lower income countries, to which our findings may be relevant.

CONCLUSION

In this structured audit procedure of 302 neonates in a paediatric hospital in Vietnam, we categorized the major causes of death/expected death as congenital malformation, prematurity and severe infections. Among the neonates with a relatively good prognosis at admission, 6 potentially avoidable risk factors were identified, which could be addressed without implementing new technologies or major organizational changes. To complete the audit cycle and address these risk factors, we suggest establishing a group to investigate possible interventions. Our findings and similar audits may be relevant to other paediatric hospitals in Vietnam and other lower income countries to decrease neonatal hospital mortality.

CONTRIBUTIONS

All authors contributed to study planning, reviewed and approved the final version of the manuscript. Review of medical files and preparation of narratives were done by PH and BH. The audits were conducted by HB, PH, AK and GG. Data management and the final analyses were done by AK. The manuscript was drafted by AK.

ACKNOWLEDGEMENT

The authors acknowledge the support from the study hospital PH1.

FUNDING

This work was supported by The Danish International Development Agency, Dagmar Marshall Fund, King Christian Xth Fund and Torben Iversens Travel Fund.

TABLES AND FIGURES

Table 1
Characteristics of the study population (n=302), n (%)

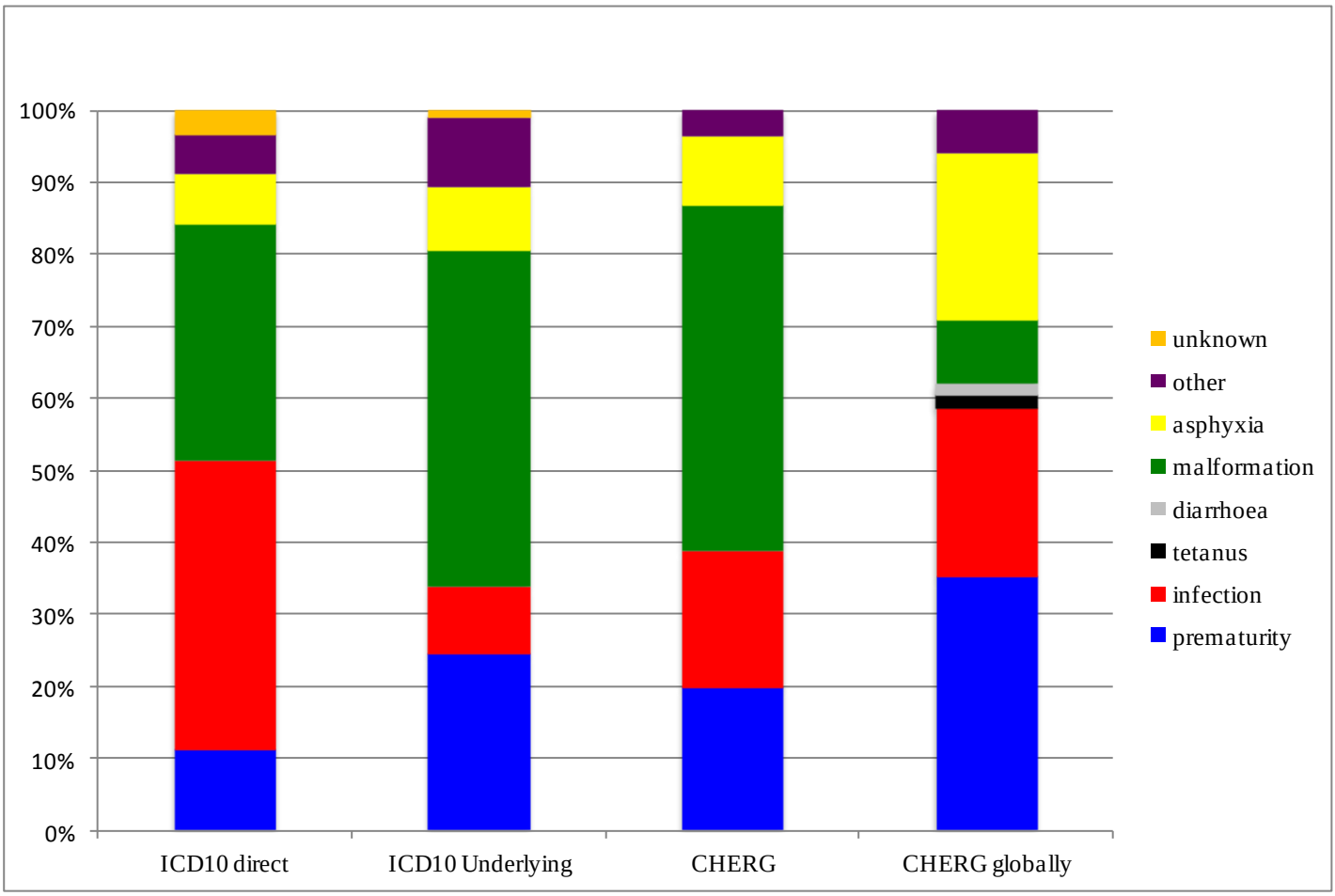
Birth weigth (gram)	
≤ 1000	13 (4)
1001 - 1500	42 (14)
1501 - 2500	97 (32)
> 2500	150 (50)
Gestational age (weeks)*	
< 28	13 (8)
28 - 31	41 (24)
32 - 36	71 (42)
≥ 37	47 (26)
Gender	
Male	181 (60)
Female	121 (40)
Admission age (days)	
0 - 1	166 (55)
2 - 7	98 (32)
8 - 28	38 (13)
Admission from	
Ho Chi Minh City	49 (16)
Provinces	253 (84)
Referral from	
From other health care facility	291 (96)
From home	11 (4)
Admission duration	
≤ 24 hours	96 (32)
> 24 hours	206 (68)
Discharge age	
0 - 1 day	38 (13)
2 - 7 days	122 (40)
8 - 28 days	142 (47)
Status at discharge	
Dead	235 (78)
Alive, WLST	67 (22)

* n = 171. WLST: withdrawal-of-life-sustaining-treatment

Figure 1

Distribution of causes of neonatal deaths (n=302)

According to ICD10 classification (direct and underlying death causes) and CHERG classification of major cause of death in PH1 and global estimates (4 million annual deaths)



Malformation, infection and prematurity caused more than 80% of the deaths/expected deaths in the hospital, according to both ICD10 and CHERG. Compared to global CHERG estimates, malformations were more frequent and prematurity was less frequent.

Table 2

Avoidable risk factors among neonates with relatively good prognosis at admission (n=71), n (%)

Relatively good prognosis at arrival defined as >50% chance of survival and normal development

Dealyed recognition and/or response to danger signs	30 (42)
Suboptimal internal transfers	26 (37)
Family and/or medical staff misperception of prognosis	25 (35)
Nosocomiel infections	24 (34)
Subopitmal septicemia management	17 (24)
Shortage of equipment usually available	12 (17)

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APPENDIX 5

Table 3 (paper II)

Table 3

Unadjusted odds ratios (OR) for predictors of death (D) and 95% co

PREDICTOR	D %	OR (95% CI)	p
SOCIO DEMOGRAPHY			
Ethnic Minority			
No	9 (170/1993)	1.00	
Yes	9 (14/159)	1.04 (0.59-1.83)	0.91
Maternal education			0.62
Primary	9 (54/624)	0.97 (0.69-1.36)	0.85
Secondary	9 (106/1187)	1.00	
Higher	7 (19/269)	0.78 (0.47-1.29)	0.33
Paternal education			0.85
Primary	9 (51/564)	1.09 (0.76-1.55)	0.65
Secondary	8 (99/1181)	1.00	
Higher	8 (24/299)	0.95 (0.60-1.52)	0.84
Siblings (number)			
<2	8 (137/1792)	1.00	
≥2	9 (20/227)	1.17 (0.71-1.91)	0.54
PREGNANCY-DELIVERY			
Antenatal care visits (number)			
<3	14 (39/283)	2.02 (1.38-2.97)	**<0.01**
≥3	7 (132/1806)	1.00	
Twin			
No	9 (186/2099)	1.00	
Yes	12 (12/97)	1.45 (0.78-2.71)	0.24
Delivery normal			
Yes	7 (67/1003)	1.00	
No	11 (123/1141)	1.69 (1.24-2.30)	**<0.01**
Gender			
Male	10 (123/1297)	1.00	
Female	8 (75/899)	0.87 (0.64-1.17)	0.36
Birthweigth (g)			**<0.01**
≤1000	35 (11/32)	6.53 (3.05 - 13.95)	**<0.01**
1001-1500	17 (36/217)	2.47 (1.63 - 3.76)	**<0.01**
1501-2500	9 (58/678)	1.17 (0.83 - 1.64)	0.38
>2500	7 (93/1252)	1.00	
Maturity (gestational weeks)			**<0.01**
< 28	38 (10/26)	6.84 (3.02 - 15.51)	**<0.01**
28-31	14 (32/235)	1.73 (1.12 - 2.65)	**0.03**
32-36	10 (45/471)	1.16 (0.79 - 1.68)	0.45
≥37	8 (91/1087)	1.00	

Table 3 (continued)

NEONATAL HISTORY			
Difficulty in breathing			
No	7 (114/1562)	1.00	
Yes	13 (84/634)	1.94 (1.44 -2.61)	**<0.01**
Color symptom			**<0.01**
Normal	8 (114/1485)	1.00	
Yellow	5 (16/331)	0.61 (0.36 - 1.05)	0.07
Blue	17 (56/337)	2.40 (1.70 - 3.38)	**<0.01**
Pale	28 (12/43)	4.66 (2.33 - 9.31)	**<0.01**
Convulsions			
No	9 (187/2125)	1.00	
Yes	16 (11/71)	1.9 (0.98-3.68)	0.05
Lack og spontanious movement			
No	9 (189/2146)	1.00	
Yes	18 (9/50)	2.27 (1.09 - 4.75)	**0.03**
Waking up difficult			
No	9 (188/2127)	1.00	
Yes	15 (10/69)	1.75 (0.88 - 3.47)	0.11
Difficulty to feed			
No	9 (161/1804)	1.00	
Yes	9 (37/392)	1.06 (0.73 - 1.55)	0.75
Feeding type			**<0.01**
Breast	6 (41/686)	1.00	
Not started	13 (100/766)	2.36 (1.61 - 3.45)	<0.01
Formula	6 (24/414)	0.97 (0.58 - 1.63)	0.90
Mixed	5 (13/274)	0.78 (0.41 - 1.49)	0.46
Stool abnormal			
No	9 (194/2125)	1.00	
Yes	6 (4/71)	0.59 (0.21 - 1.65)	0.32
Symptom duration (days)			
≤1	11 (136/1256)	1.00	**<0.01**
>1	6 (49/847)	0.52 (0.36 - 0.71)	
Transport duration (hours)			**0.04**
0-1	8 (68/809)	1.00	
2-5	12 (91/788)	1.42 (1.02-1.98)	**0.04**
≥6	7 (14/201)	0.82 (0.45-1.48)	0.50

Table 3 (continued)

CLINICAL ADMISSION CONDITION			
Admission age (days)			**<0.01**
0-1	12 (111/933)	1.00	
2-7	9 (62/691)	0.73 (0.53-1.01)	0.06
8-28	4 (25/572)	0.34 (0.22-0.53)	**<0.01**
Color sign			**<0.01**
Pink	6 (88/1487)	1.00	
Jaundice	8 (31/412)	1.29 (0.85 - 1.98)	0.24
Cyanosis	31 (56/185)	6.90 (4.72 - 10.10)	**<0.01**
Pale	28 (17/61)	6.14 (3.37 - 11.19)	**<0.01**
Temperature (C)			**<0.01**
<34	30 (3/10)	5.43 (1.38 - 21.25)	**0.02**
34-35.9	28 (26/94)	4.85 (2.98 - 7.87)	**<0.01**
36-38	7 (131/1791)	1.00	
>38	11 (20/188)	1.51 (0.92 - 2.48)	0.11
Conciseness			
Awake	5 (87/1749)	1.00	
Lethargy-Unconcious	29 (101/348)	7.81 (5.69 - 10.72)	**<0.01**
Respiratory Failure*			
No	6 (126/1982)	1.00	
Yes	46 (65/142)	12.43 (8.54 - 18.11)	**<0.01**
Respiratory rate**			**<0.01**
<34	16 (3/19)	3.31 (0.94 - 11.62)	0.06
34-57	5 (73/1362)	1.00	
>57	8 (50/601)	1.60 (1.10 - 2.33)	**0.01**
Grunting**			
No	6 (98/1766)	1.00	
Yes	12 (20/176)	2.18 (1.31 - 3.63)	**<0.01**
Chest retraction**			**<0.01**
No	4 (52/1325)	1.00	
Moderate	9 (50/529)	2.55 (1.71 - 3.82)	**<0.01**
Severe	14 (20/145)	3.91 (2.27 - 6.77)	**<0.01**
Shock***			
No	7 (147/2064)	1.00	
Yes	54 (42/78)	15.2 (9.45 - 24.48)	**<0.01**

*Respiratory failure defined as gasping/prolonged apnea/intubation/bagging

** If no respiratory failure

*** Shock defined as minimum 2 out of 3 (tachycardia/bradycardia, prolonged capillary refill tir