The 15th Database Quality Improvement Conference
Program

Date : September 25, 2021

Venue: Zoom (ID: 869 2435 6061 PW: 20210925)

10:30-10:35 (JST)

Opening remark

Satoshi Kusuda

Kyorin University

10:35-11:00

Annual report

Satoshi Kusuda

Kyorin University

11:00-11:50

Clinical Trials in Newborn Infants - The Case for URGENT International Collaboration

Prof. Ju Lee Oei

The Royal Hospital for Women

University of New South Wales

Australia

11:50-12:40

Trends in outcomes among very low birth weight infants in Japan from NRNJ database

Masanori Fujimura

Osaka Women's and Children's Hospital

12:40-13:10

Lunch

13:10-13:20

Guidance on changes of variables of database (Japanese)

Satoshi Kusuda

Kyorin University

13:20-14:50

Learn from hospitals with lowest incidence of sepsis among extremely preterm infants (Japanese)

Moderators

Shinya Hirano　Osaka Women's and Children's Hospital

Hidehiko Nakanishi　Kitasato University

Tetsuya Isayama　National Institute for Child Health and Development

Presenters

Akita　Red Cross Hospital

Anjo Kosei Hospital

Niigata City Hospital

14:50-15:00

Final results of INTACT study (Japanese)

Satoshi Kusuda

Kyorin University

15:00

Closing remarks

Neonatal Network Database: Annual Report

Neonatal Research Network of Japan

Satoshi Kusuda

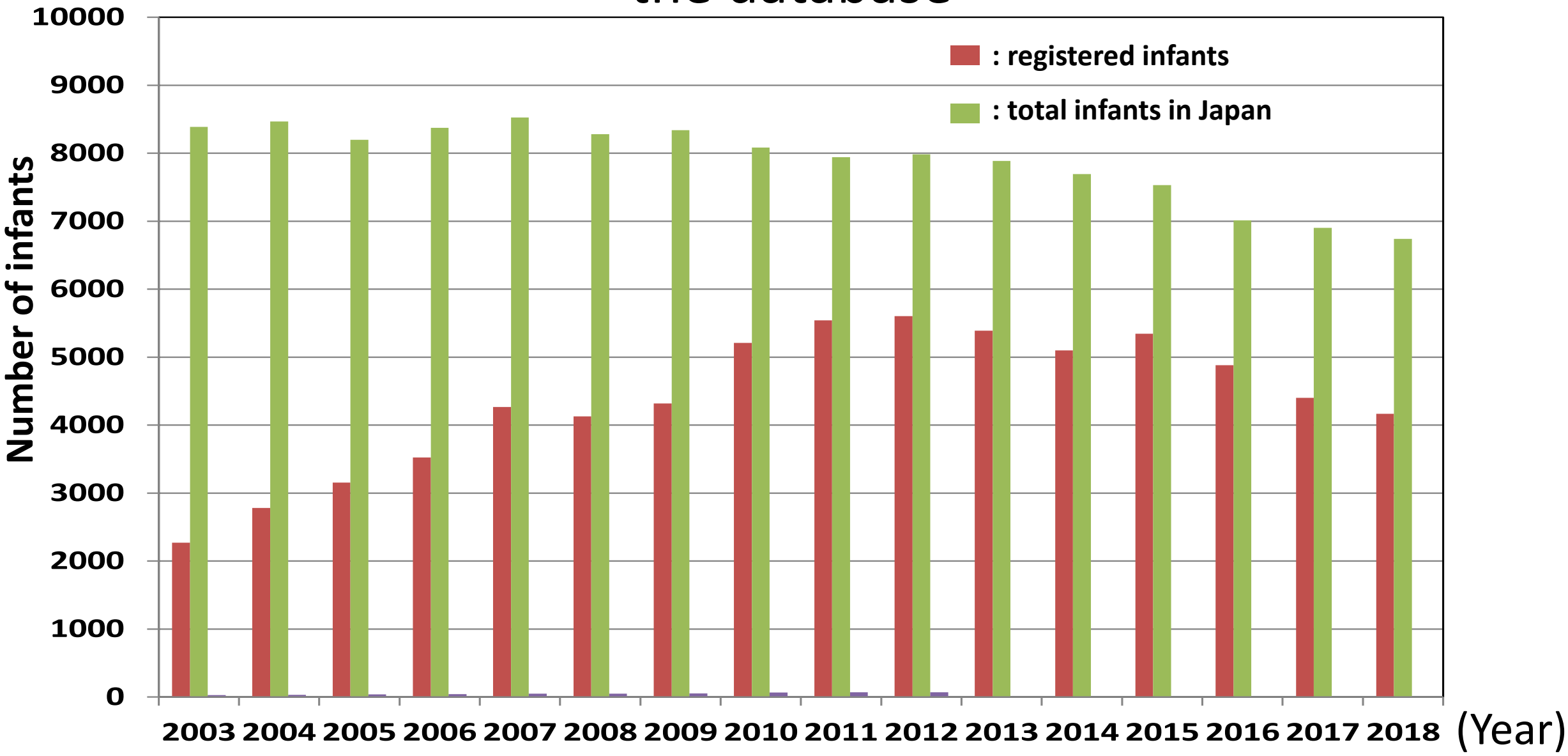
Development of the network database for VLBW infants in Japan

- Infants weighing at or less than 1500g
  (including all infants born before 32 GW since 2014)
- Definition of diseases and interventions in the operation manual.
- Morbidities collected until discharge from NICU
- Follow-up data at 1.5, 3 , and 6years of age
- Started in 2003

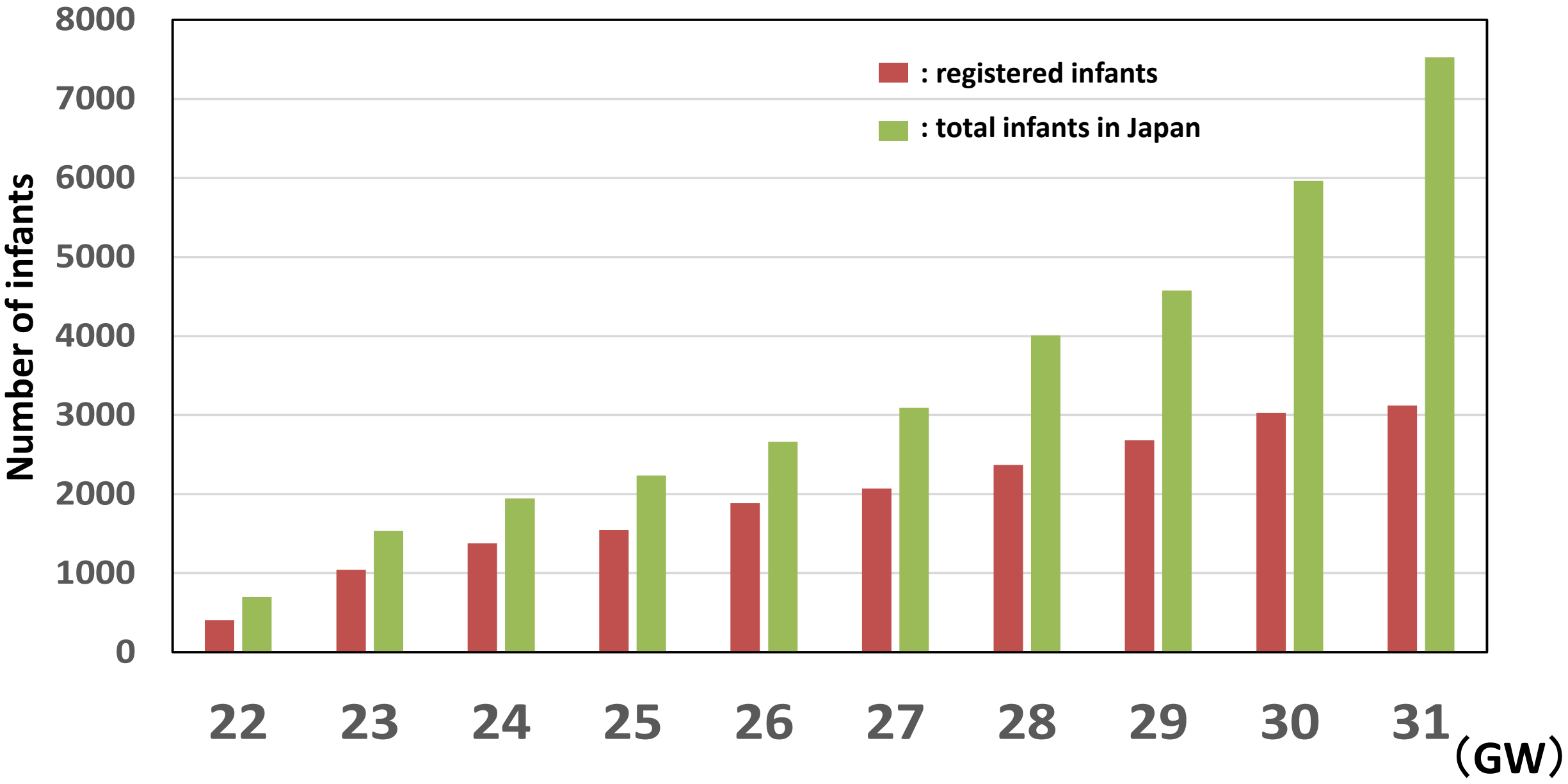
Annual Report 2021

- Data summarized between 2003 and 2018.
- All analyzed data are available online (http://plaza.umin.ac.jp/nrndata/).
- Facility names are anonymous.
- Number of facilities participating is 220.
- Total number of registered infants is 76,444.
- In 2018, 4,154 infants were registered.

Number of infants born in Japan vs registered infants in the database



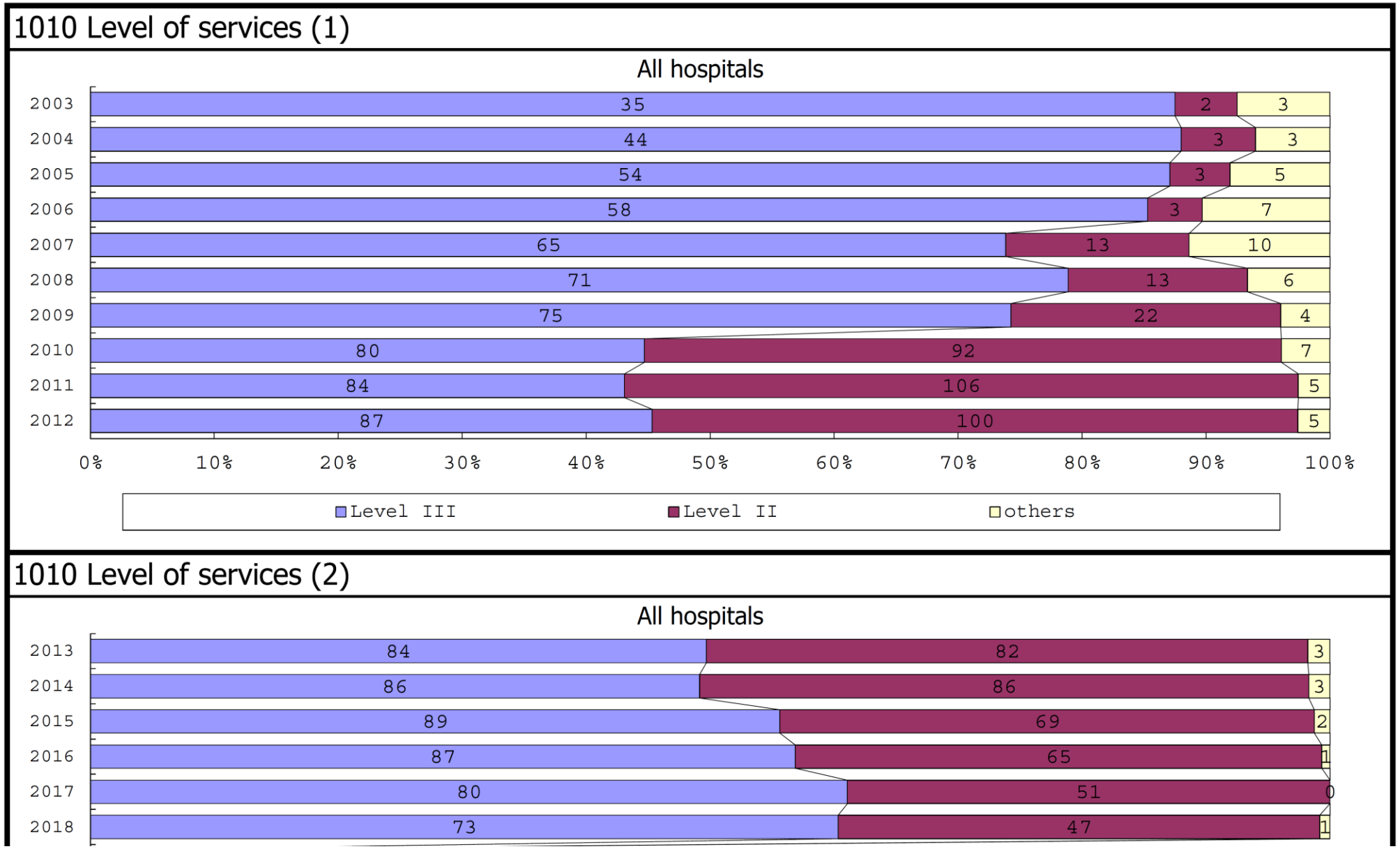
Coverage of NRNJ database by GW last 5 years



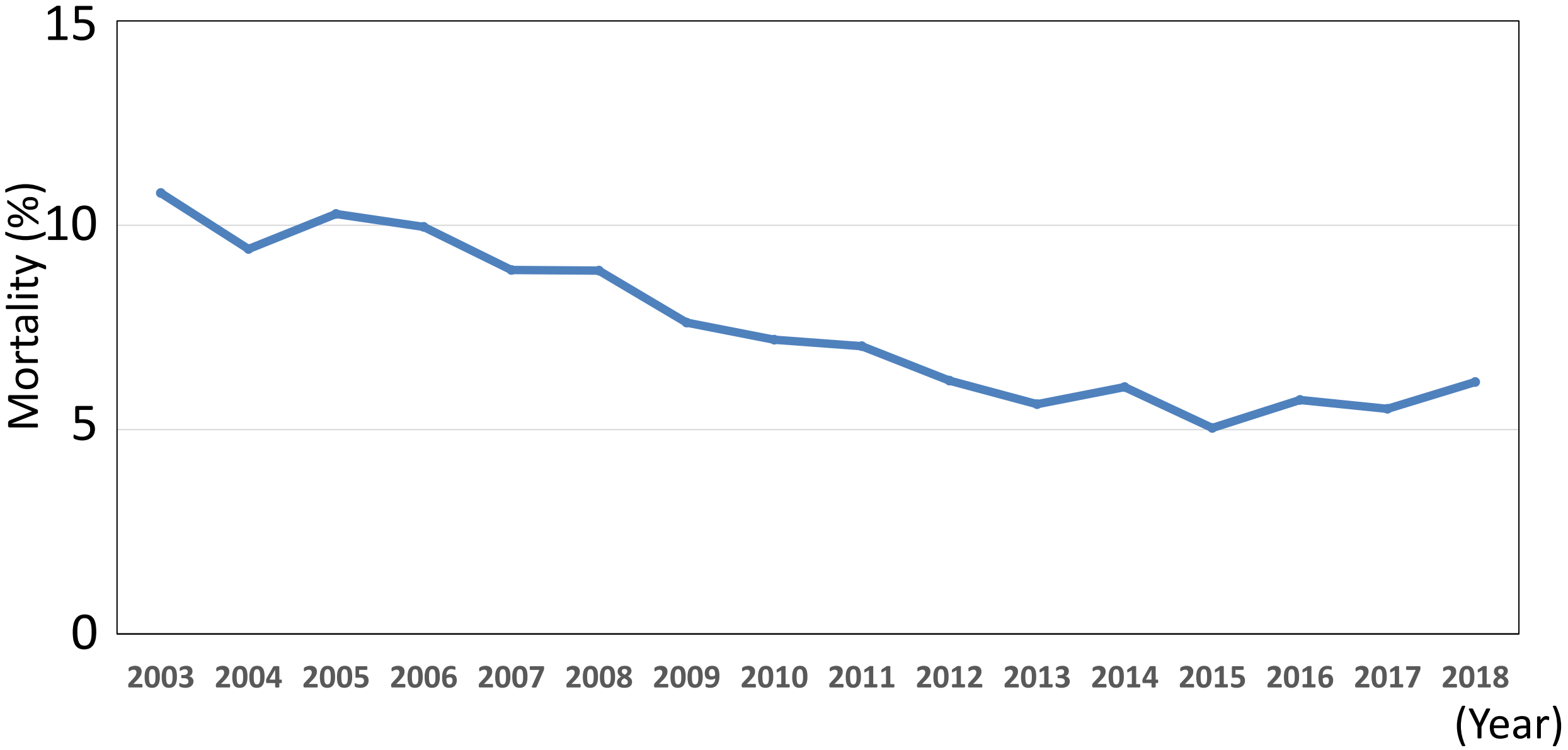
Participating hospitals（as of year 2018）

Sapporo City Hospital	Yokosuka Kyosai Hospital	
Asahikawa Kosei Hospital	Odawara City Hospital	National Cerebral and Cardiovascular Center
Engaru Kosei Hospital	Nippon Medical School Musashi Kosugi Hospital	Kitano Hospital
Kushiro Red Cross Hospital	Yokohama City Hospital	Saiseikai Suita Hospital
Obihiro Kosei Hospital	Saiseikai Eastern Yokohama Hospital	Chifune Hospital
Tenshi Hospital	Yokohama Medical Center	Bell Land General Hospital
NTT East Sappro Hospital	Yamanashi Prefecture Central Hospital	Rinku General Hospital
Nikko Kinen Hospital	Nagano Children's Hospital	Osaka Red Crsoo Hospital
Nayoro City Hospital	Shinshu University	Yao City Hospital
Sapporo Prefecture Medical University	Iida City Hospital	Hannan Central Hospital
Asahikawa Medical University	National Shinshu Ueda Medical Center	Osaka General Medical Center
Aomori Prefecture Central Hospital	Saku General Hospital	Osaka City University
Iwate Medical University	Nigata University	Kobe Children's Hospital
Iwate Prefecture Ohfunato Hospital	Niigata Central Hospital	Kobe University
Iwate Prefecture Kuji Hospital	Niigata City Hospital	Kakogawa City Hospital
Iwate Prefecture Ninohe Hospital	Nagaoka Red Cross Hospital	Saiseikai Hyogo Hospital
Sendai Red Cross Hospital	Koseiren Takaoka Hospital	Kobe City Medical Center Central Hospital
Tohoku University	Toyama Prefectural Central Hospital	Hyogo Medical University
Akita Red Cross Hosptai	Toyama University	Himeji Red Cross Hospital
Akita University	Ishikawa Prefectural Central Hospital	Toyooka General Hospital
Tsuruoka City Shonai Hospital	Kanazawa Medical University	Hyogo Prefectural Awaji Medical Center
Yamagata University	Kanazawa Medcial Center	Nara Prefecture Medical University
Yamagata Prefecture Central Hospital	Fukui Prefectural Hospital	Wakayama Prefecture Medical University
Fukusima Prefecture Medical University	Fukui University	Tottori Prefectural Central Hospital
Takeda General Hospital	Gifu Prefectural Medical Center	Tottori University
National Fukushima Hospital	Oogaki City Hospital	Shimane Prefectural Central Hospital
Tsukuba University	National Nagara Medical Center	Matue Red Cross Hospital
Tsuchiura Kyodo Hospital	Takayama Red Cross Hospital	Kurashiki Central Hospital
Ibaraki Children's Hospital	Seirei Hamamatsu Hospital	Tsuyama Central Hospital
Dokkyo Medical University	Shizuoka Saiseikai Hospital	Kawasaki Medical University
Jichi Medical University	Shizuoka Children's Hospital	National Okayama Medical Cneter
Ashikaga Red Cross Hospital	Hamamatsu Medical University	Okayama Red Cross Hospital
Gunma Prefecture Children's Hospital	Numazu City Hospital	Hiroshima City Central Hospital
Kiryu Kosei General Hospital	Yaizu City Hospital	Hiroshima Prefectural Hospital
Ohta General Hospital	Fujieda City Hospital	Hiroshima University
Gunma University	Nagoya Red Cross Daini Hospital	Tsuchiya General Hospital
Saitama Medical University	Nagoya University	National Kure Medical Center
Saitama Prefecture Children's Hospital	Nagoya Red Cross Daiici Hospital	Yamaguchi University
National Nishisaitama Central Hospital	Toyohashi City Hospital	Yamaguchi Prefecture Medical Center
Saitama Medical University Medical Center	Nagoya City Seibu Medical Cneter	Tokushima University
Kawaguchi City Medical Center	Fujita Medical University	Tokushima City Hospital
Jichi Medical University Saitame Medical Center	Anjokosei Hospital	Kagawa University
Asahi Central Hospital	Koritsu Tosei Hospital	Shikoku Medical Center for Children and Adults
Chiba City Kaihin Hospital	Komaki City Hospital	Matsuyama Red Cross Hospital
Kameda General Hospital	Toyota Memorial Hospital	Ehime Prefectural Cntral Hospital
Tokyo Women's Medical University Yachiyo Medical Center	Okazaki City Hospital	Kochi Health Science Center
Juntendo University Urayasu Hospital	Handa City Hospital	Saint Maria Hospital
Narita Red Cross Hospital	Konankosei Hospital	National Kyushu Medical Center
Tokyo Metropolitan Children's Medcial Center	Nogoya Chity University	Kurume University
Tokyo Women's Medical University	Aichi Medical University	Kitakyushu City Hospital
Aiiku Hospital	National Mie Cnetral Medical Center	University of Occupational and Environmental Health Japan
Nihon University	Ise Red Cross Hospital	Fukuoka University
National International Medical Center	Yokkaichi City Hospital	Kyushu University
Tokyo Medical Universtity	Otsu Red Cross Hospital	Iizuka Hospital
Teikyo University	Shiga Medical University	National Kokura Medical Center
Showa University	Nagahama Red Cross Hospital	Fukuoka City Children's Hospital
Japan Red Cross Hospital	Uji Tokushukai Hospital	National Saga Hospital
National Center for Child Health and Development	Japan Baptist Hospital	Nagasaki University
Tokyo Metropolitan Otsuka Hospital	Kyoto University	National Nagasaki Medical Cneter
Tokyo University	Kyoto Red Cross Daiichi Hospital	Saseho City Hospital
Toho University	National Maizuru Medical Center	Kumamoto City Hospital
Tokyo Metropolitan Bokuto Hospital	Fukuchiyama City Hospital	Kumamoto University
Tokyo Jikei Medical University	Kyoto Prefecture Medical University	Oita Prefectural Hospital
Tokyo Medical and Dental University	Kyoto City Hospital	Almeida Memorial Hospital
Saint Luku Hospital	Mitubishi Kyoto Hospital	Nakatsu City Hospital
Juntendo University	Yodogawa Christian Hospital	Miyazaki University
Sanikukai Hospital	Osaka Women's and Children's Hospital	National Miyakonojo Hospital
Katsushika Red Cross Hospital	Osaka University	Kagosima City Hospital
Yokohama Rosai Hospital	Takatuski General Hospital	Imakyure General Hospital
Yokohama City Universtiy Medical Center	Kansai Medical University	Okinawa Prefectural Nanbu Medcial Center/Nanbu Child Medical Center
Marianna Medical University	Osaka City General Hospital	Okinara Prefectural Central Hospital
Kanagawa Children's Medical Center	Osaka City Sumiyoshi Hospital	Naha City Hospital
Tokai University	Aizenbashi Hospital	Okinawa Red Cross Hospital
Kitazato University	Toyonaka City Hospital	

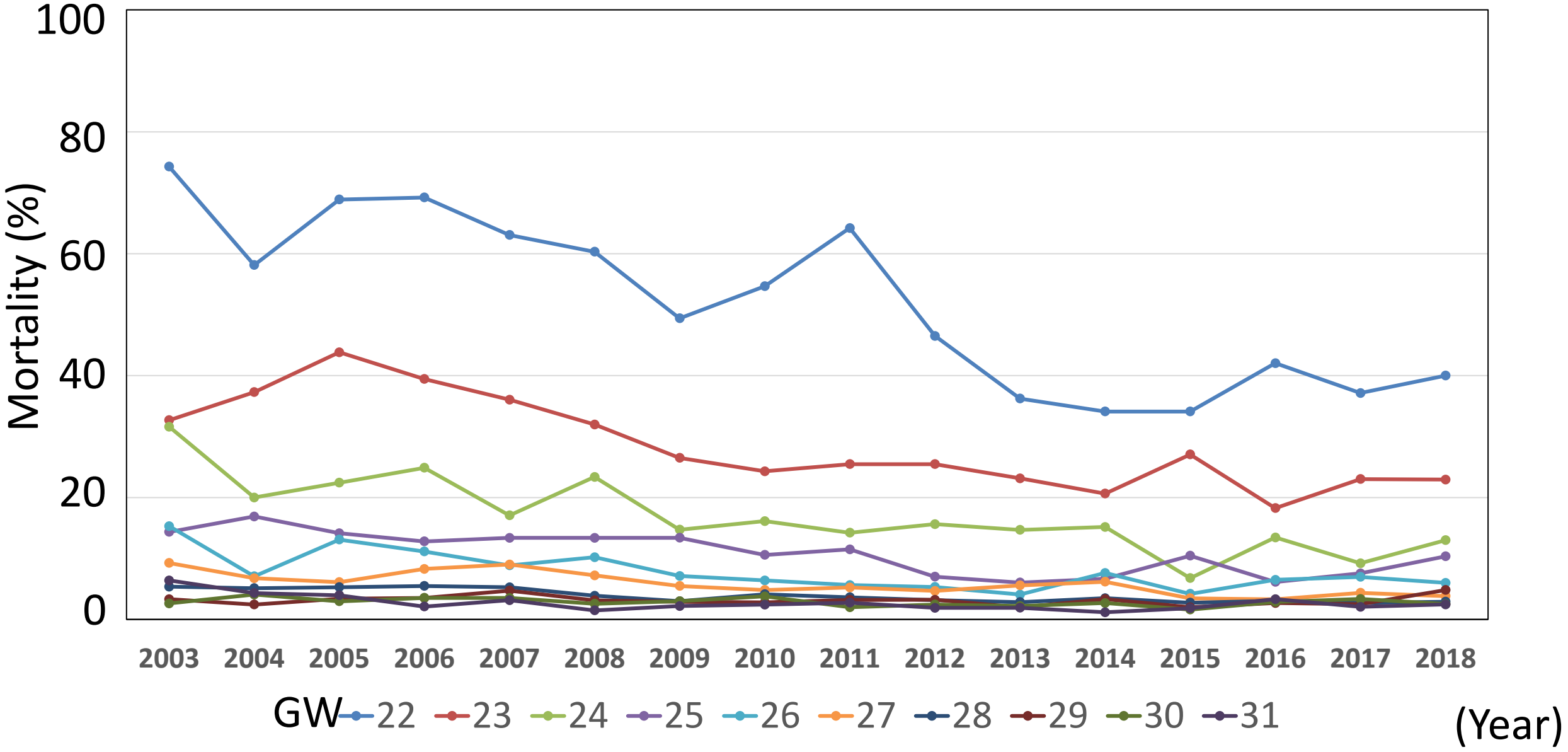
Trends in Levels of participating hospitals



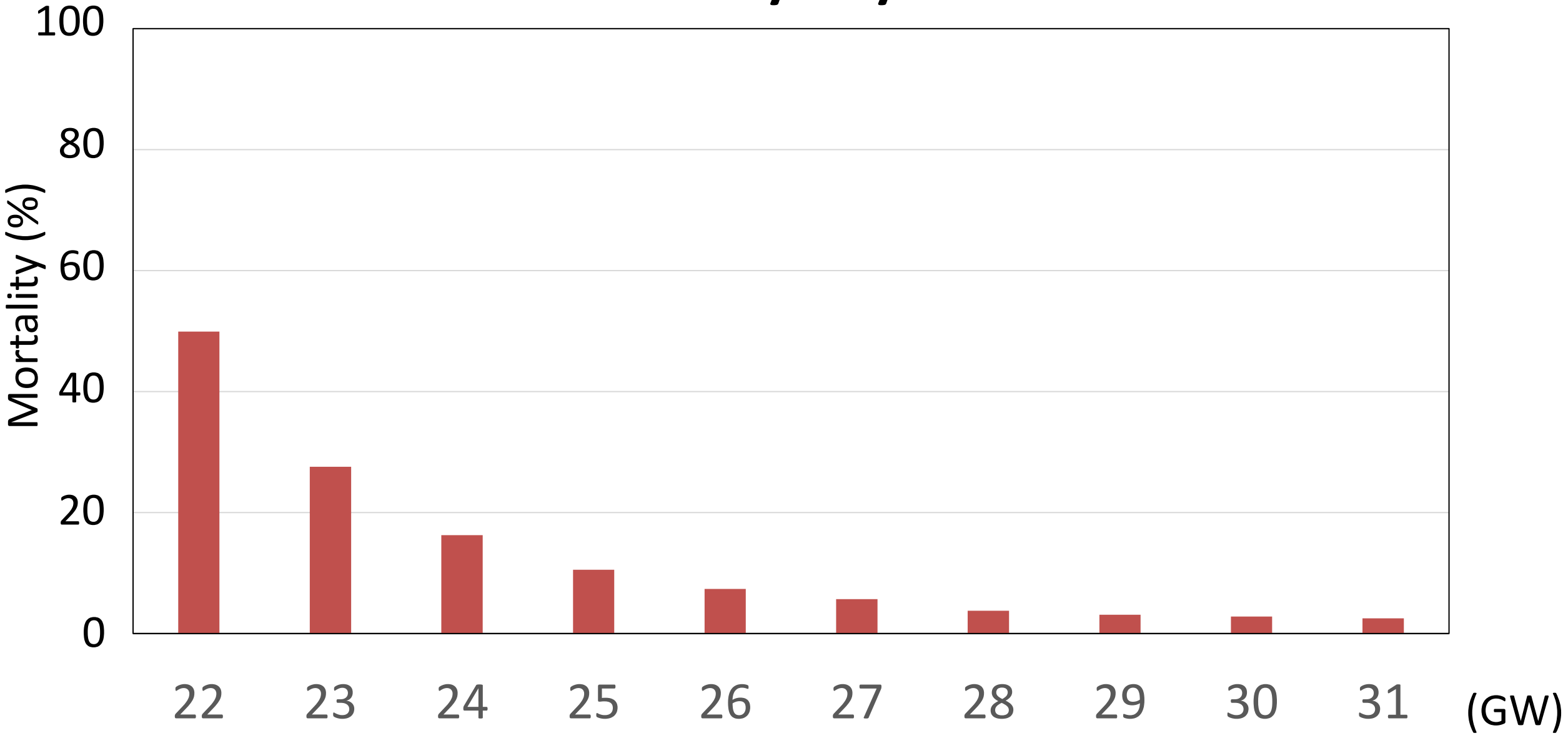
Trends in Mortality



Trends in Mortality by GW

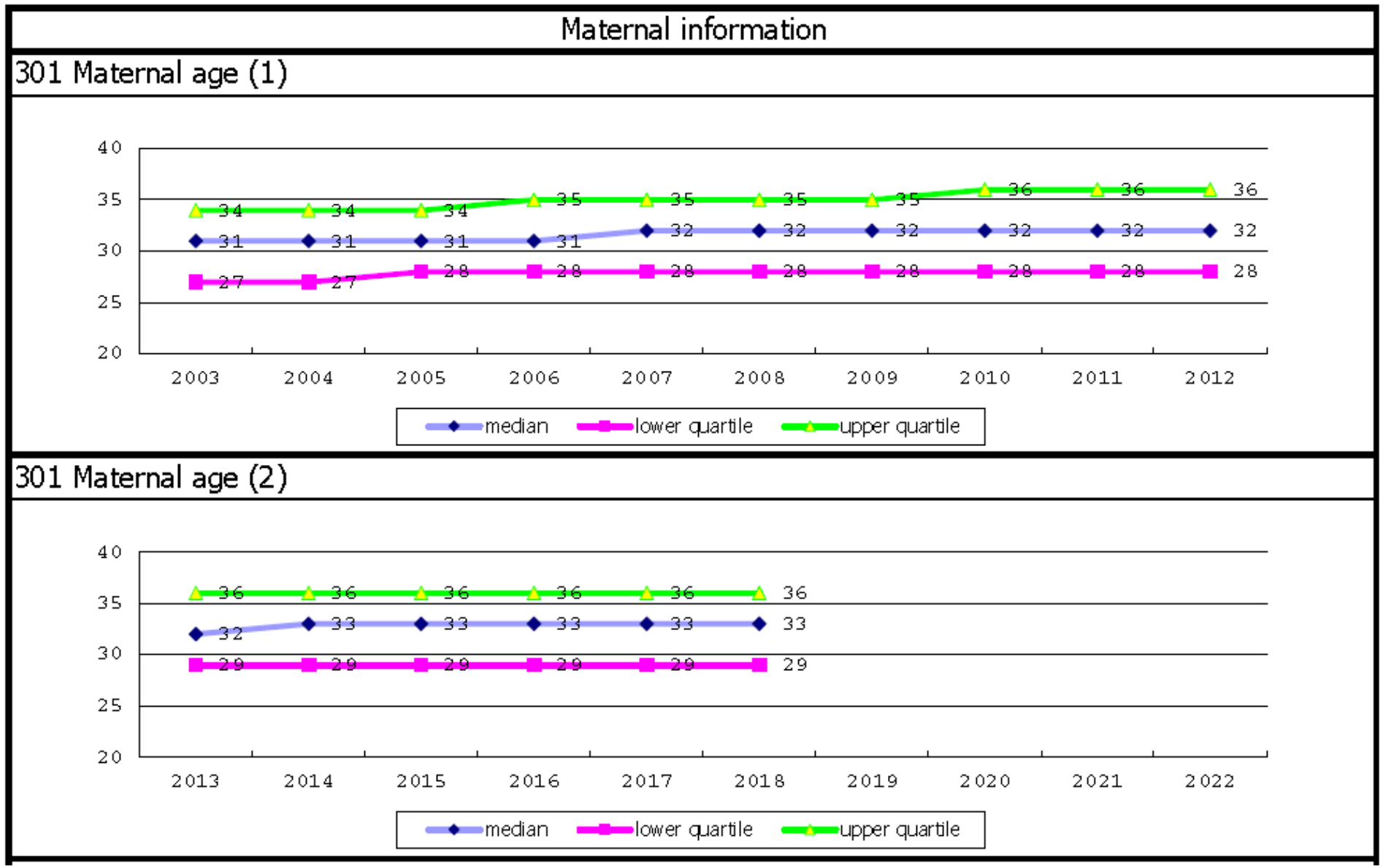


Mortality by GW

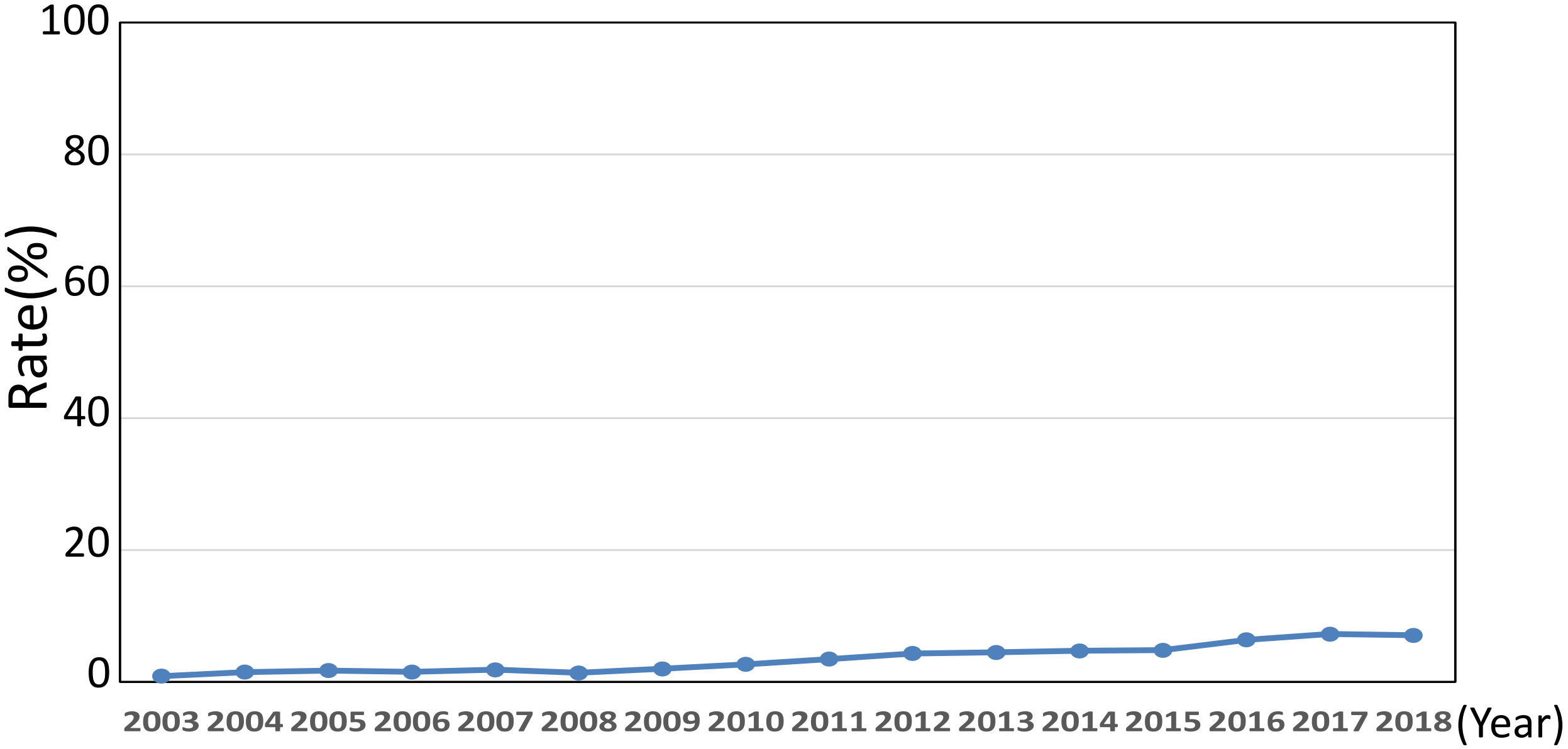


Trends in Japanese network

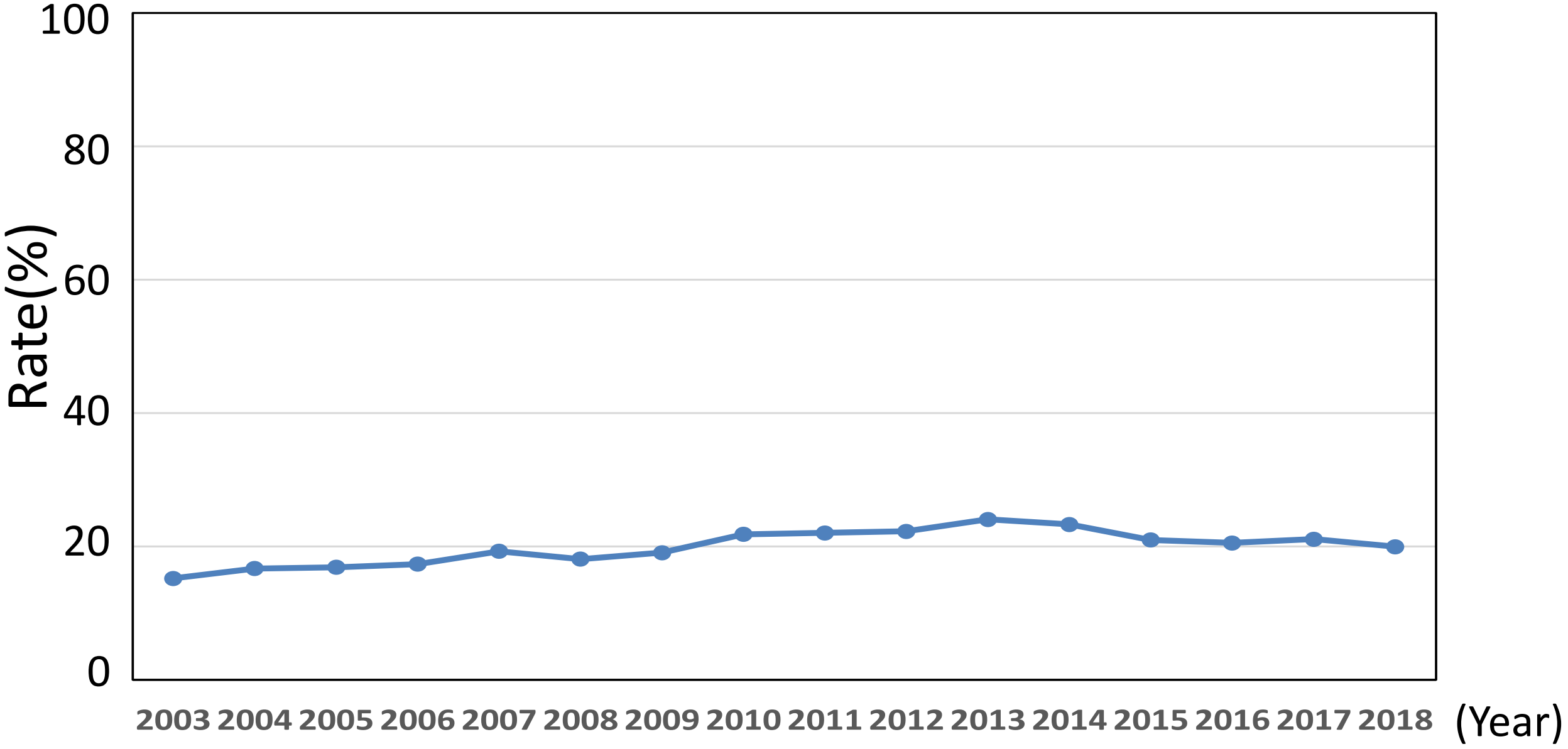
Trends in maternal age



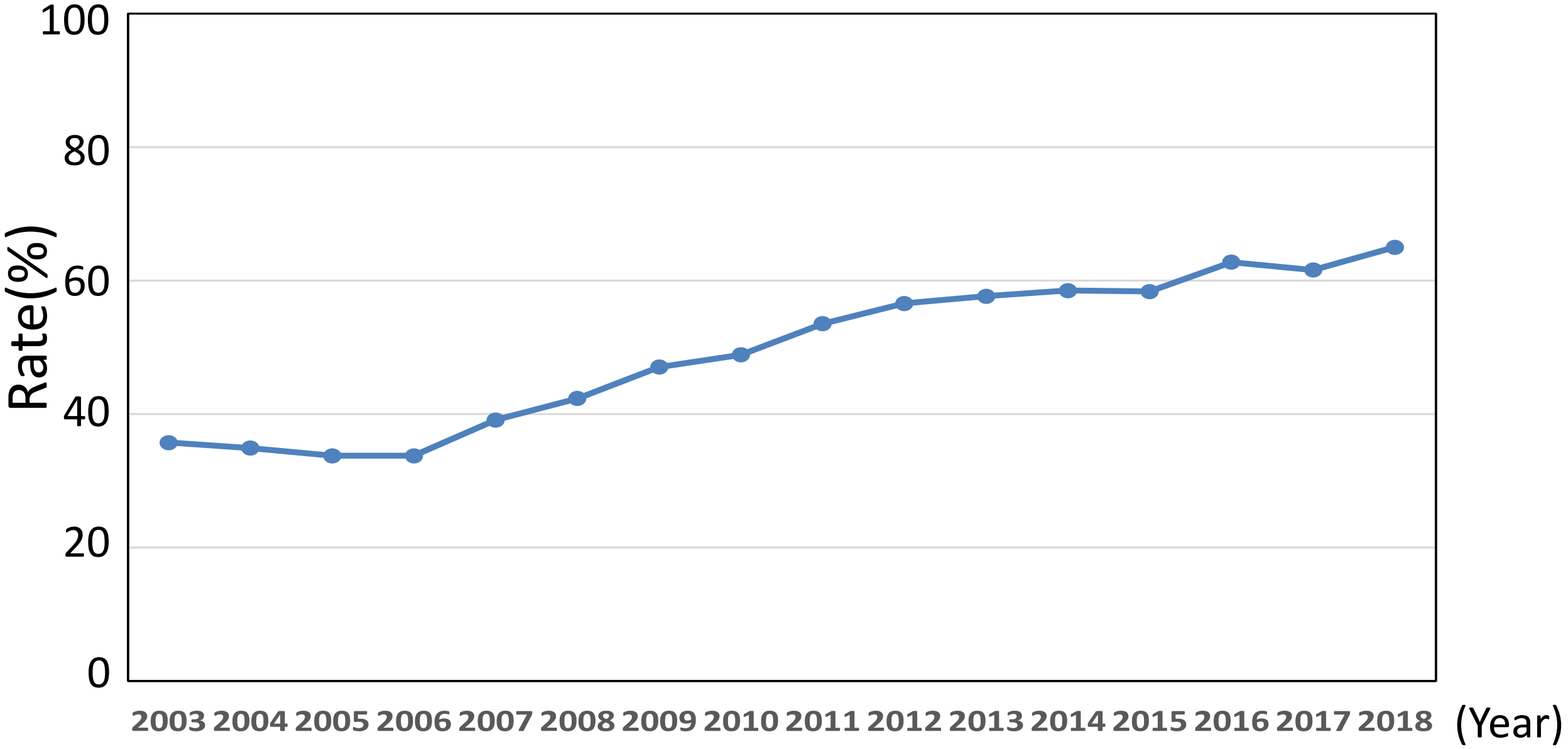
Trends in maternal diabetes mellitus



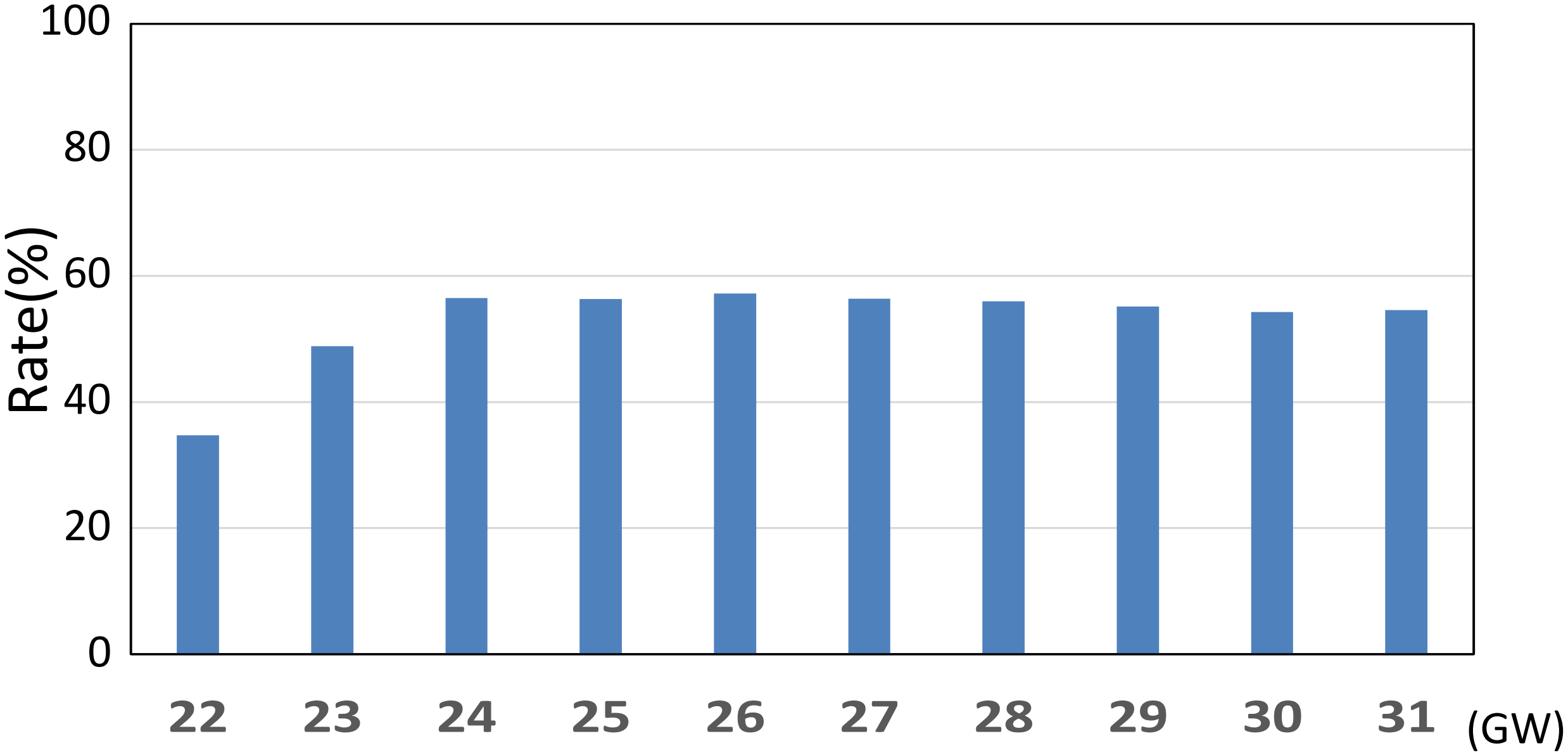
Trends in maternal hypertensive disorders



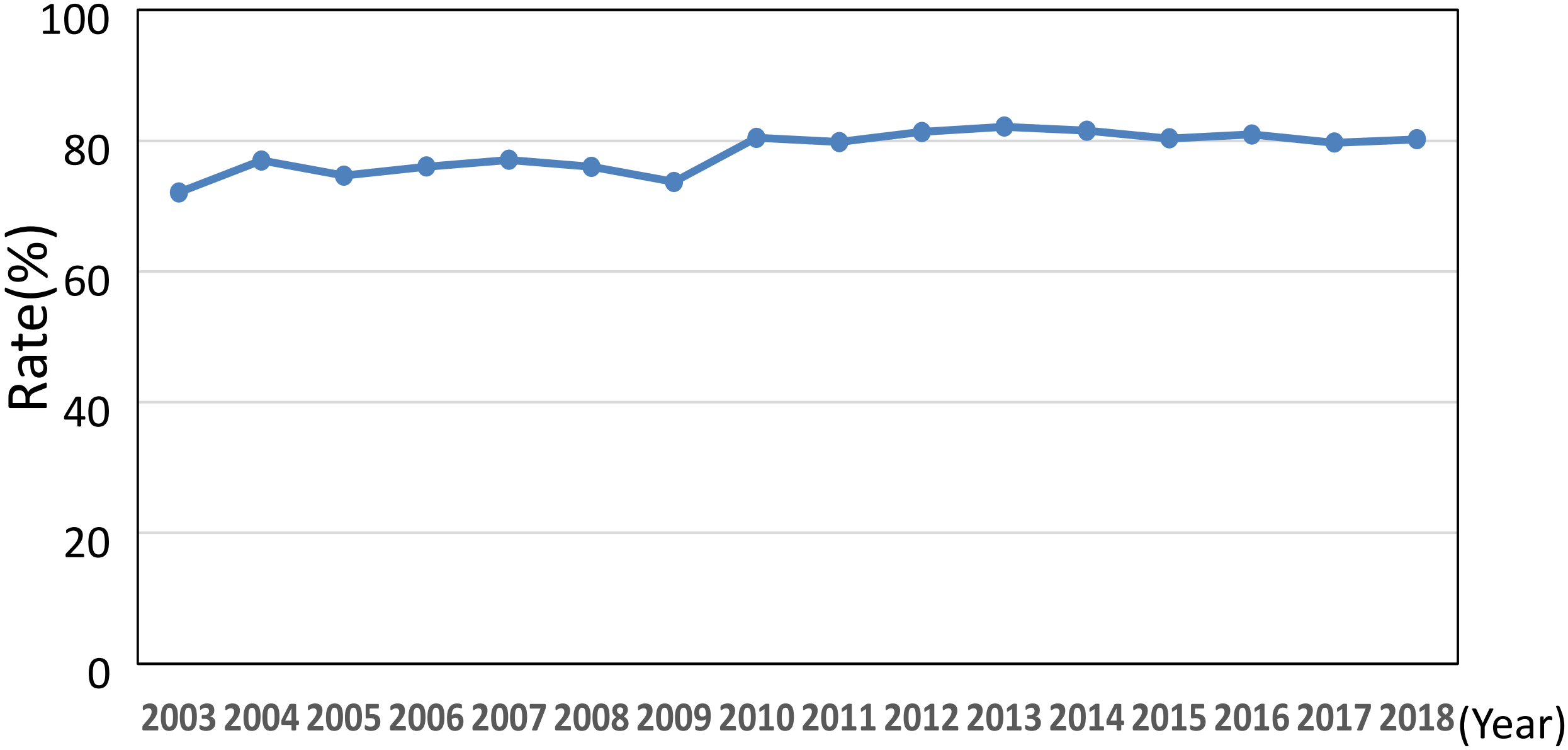
Trends in maternal glucocorticoid use



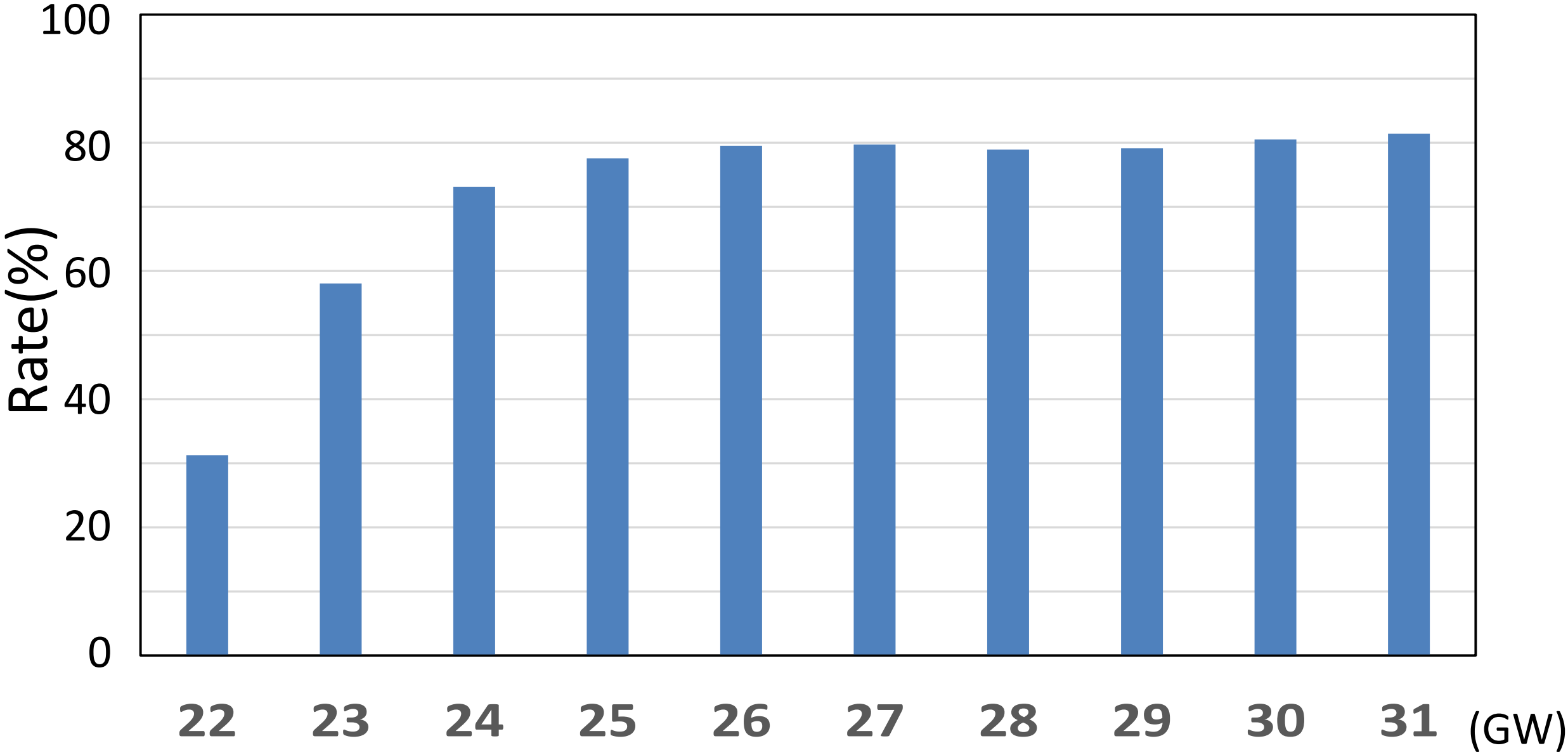
Maternal glucocorticoid use rates by GW



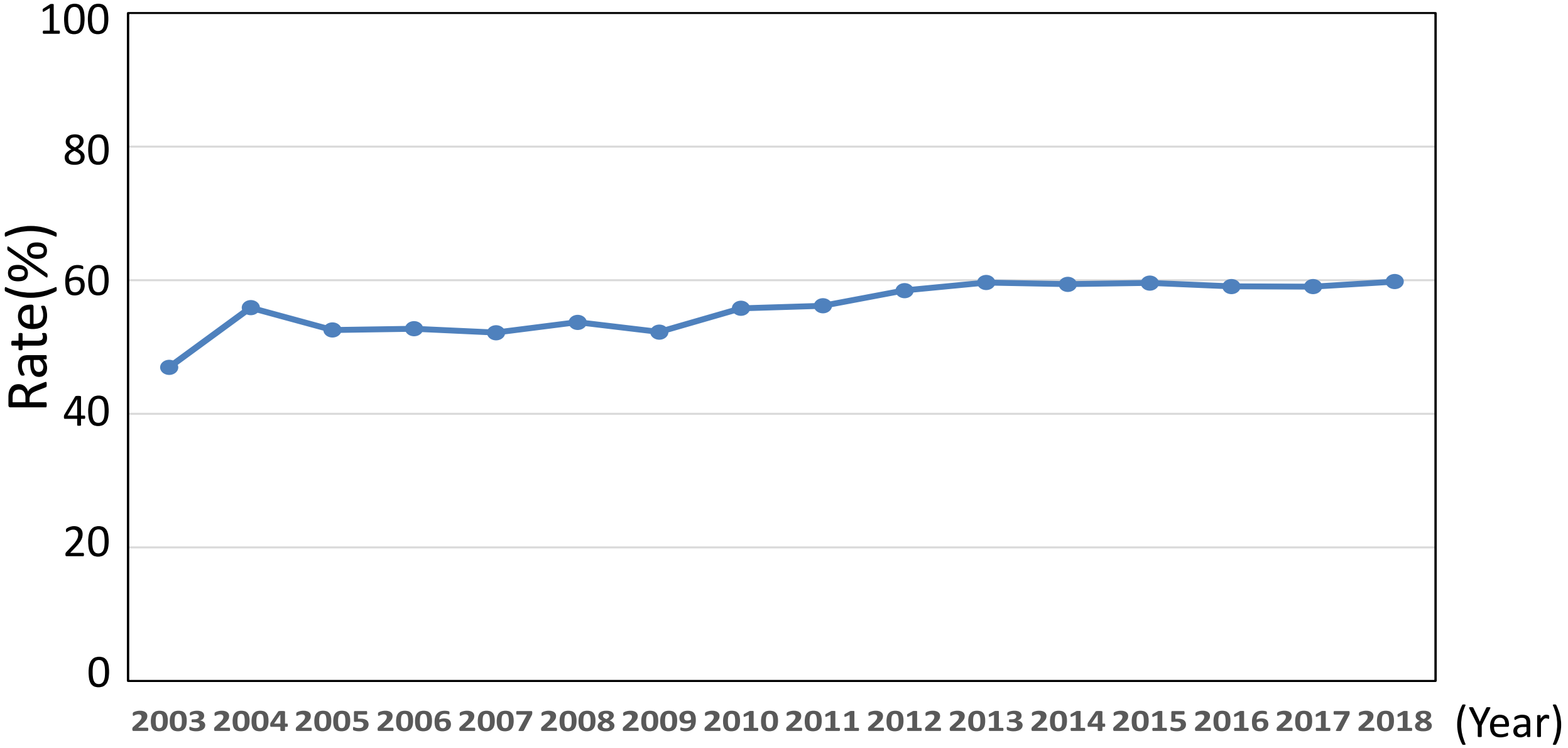
Trends in Cesarean delivery rates



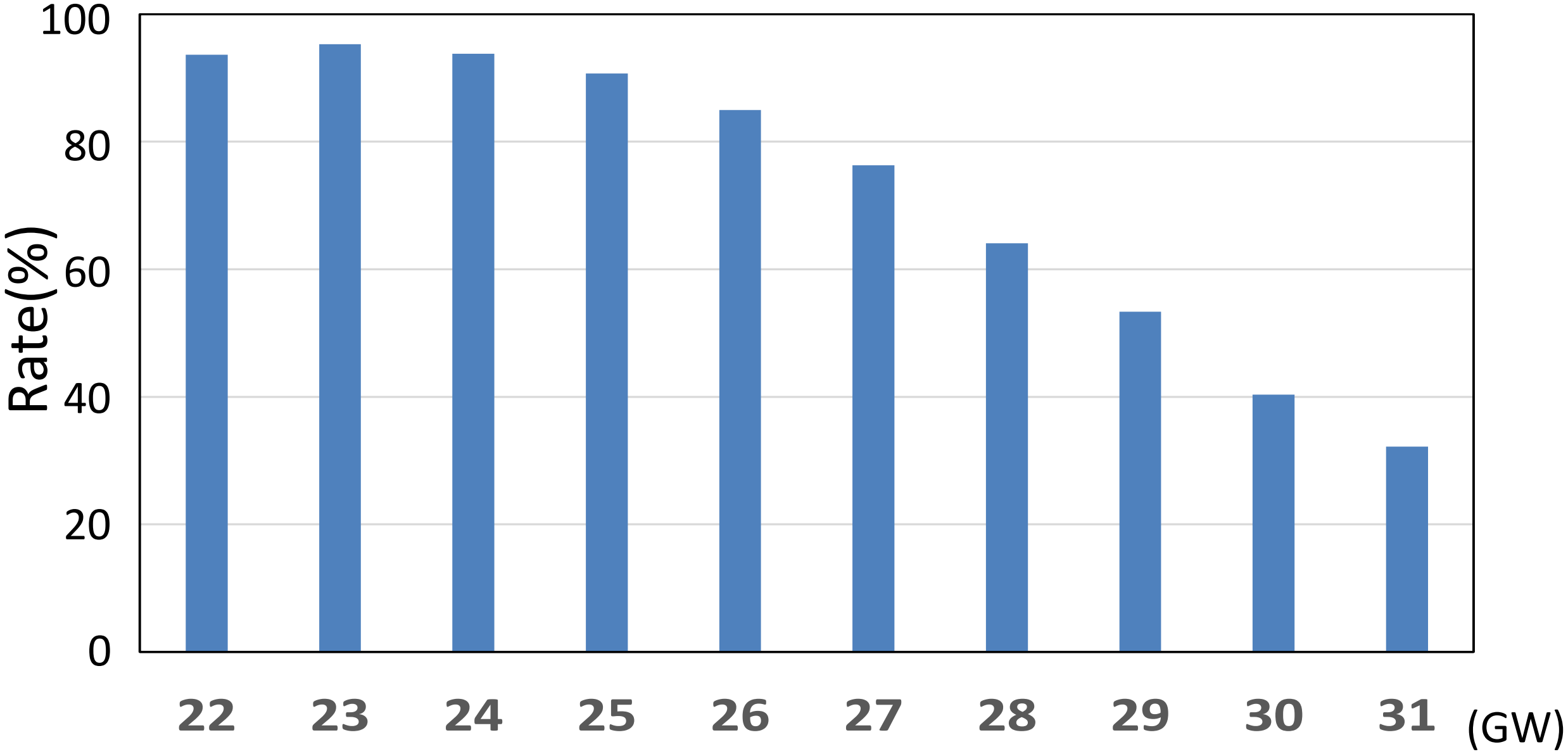
Cesarean delivery rate by GW



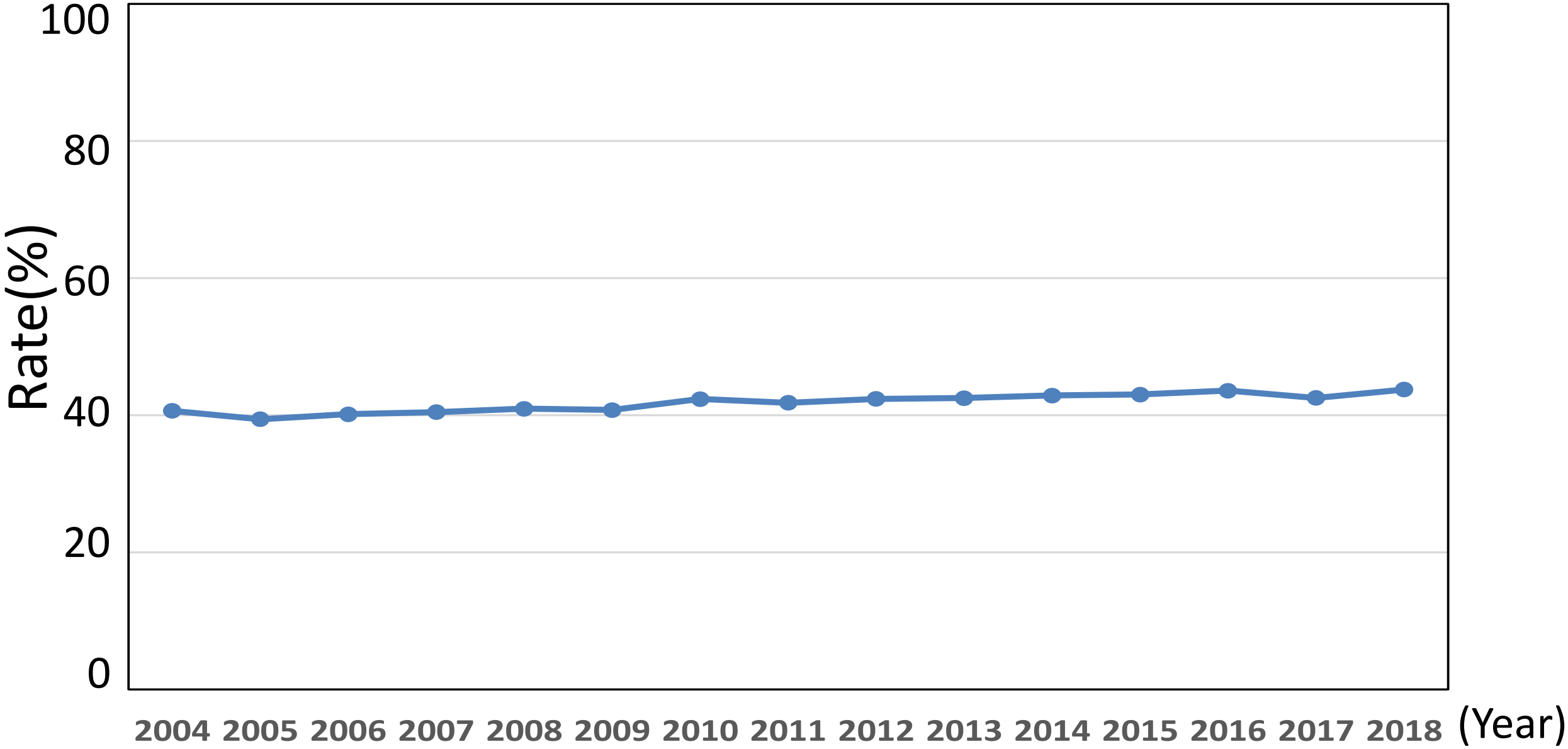
Trends in tracheal intubation rates at birth



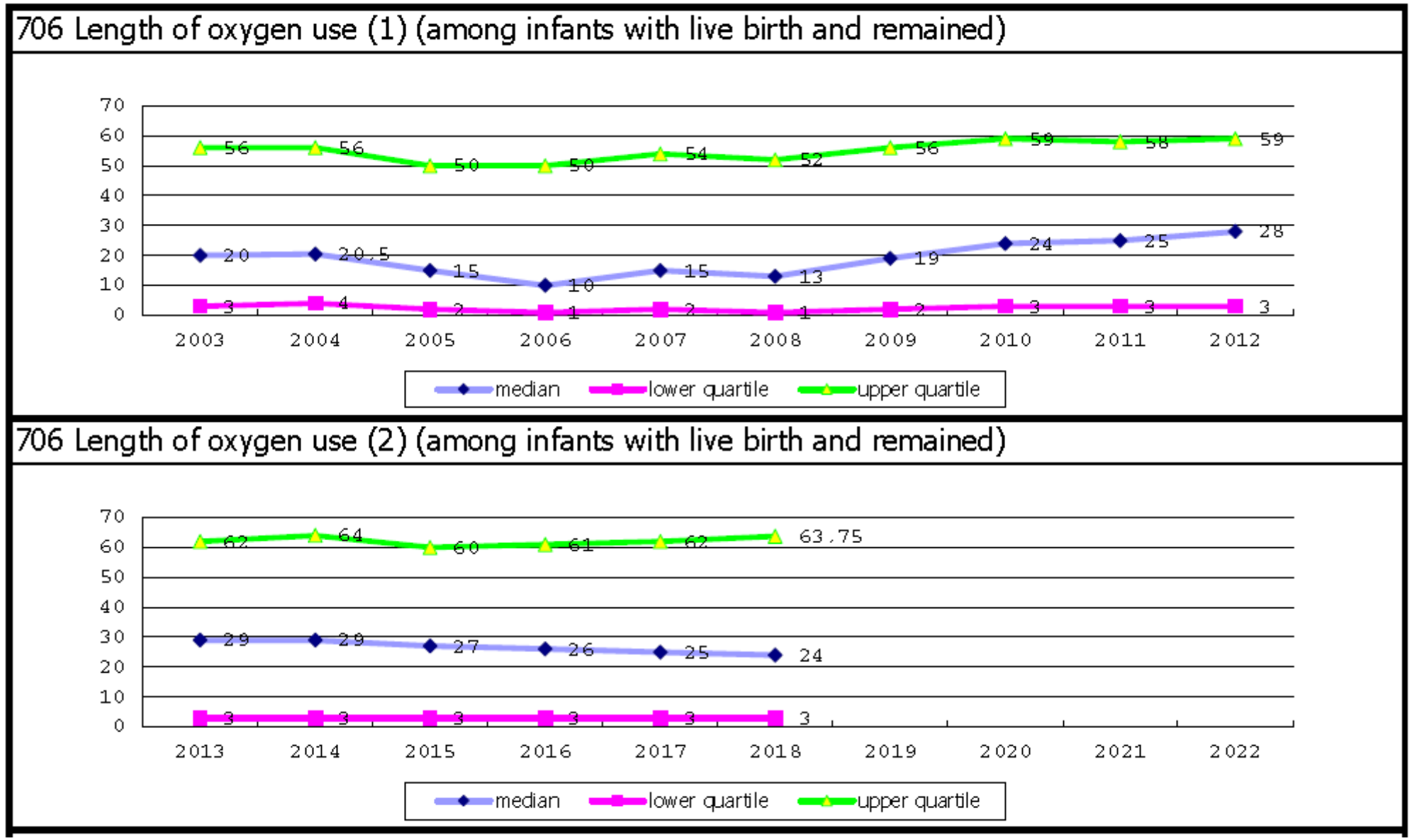
Tracheal intubation rate by GW



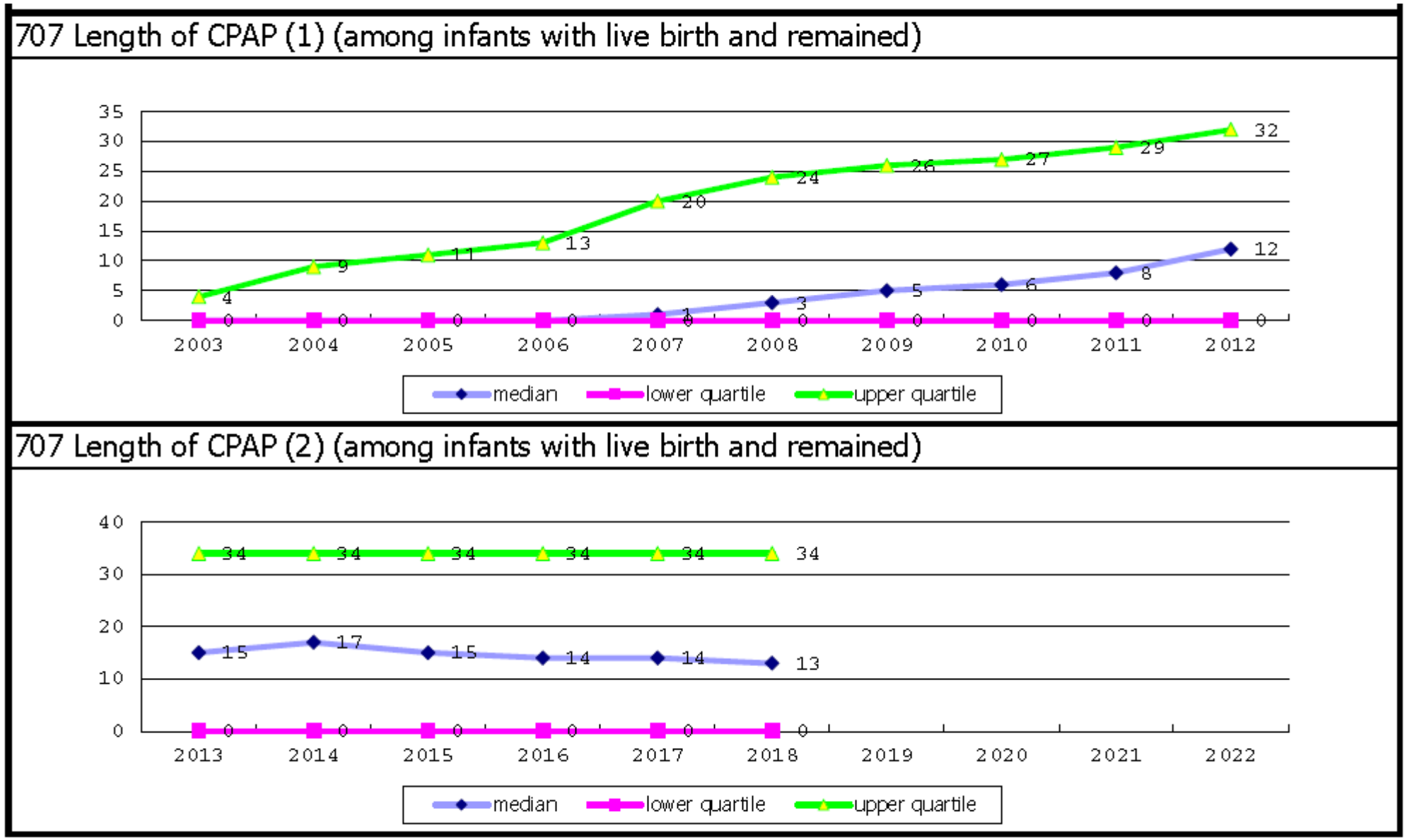
Trends in rates of RDS



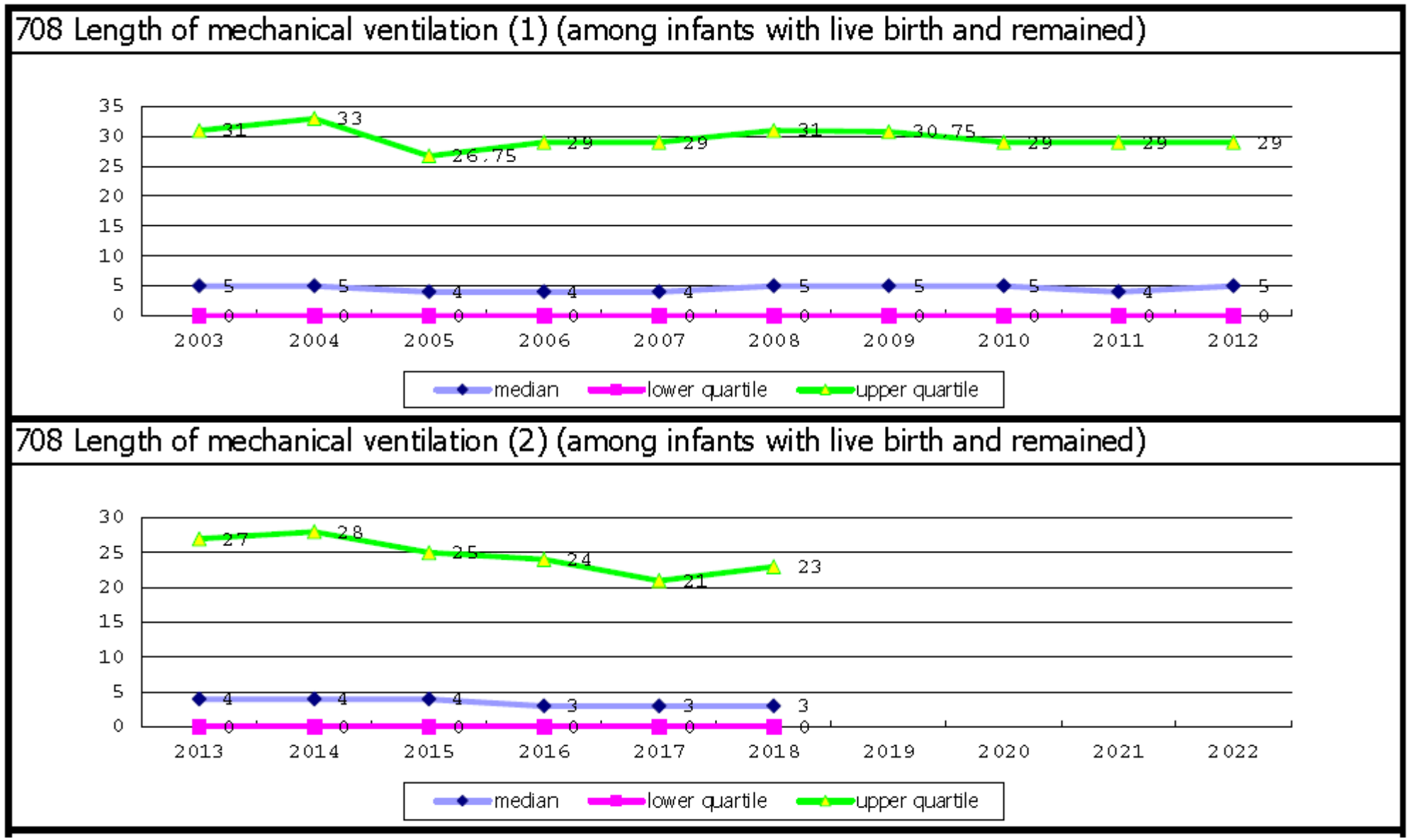
Trends in length of oxygen use



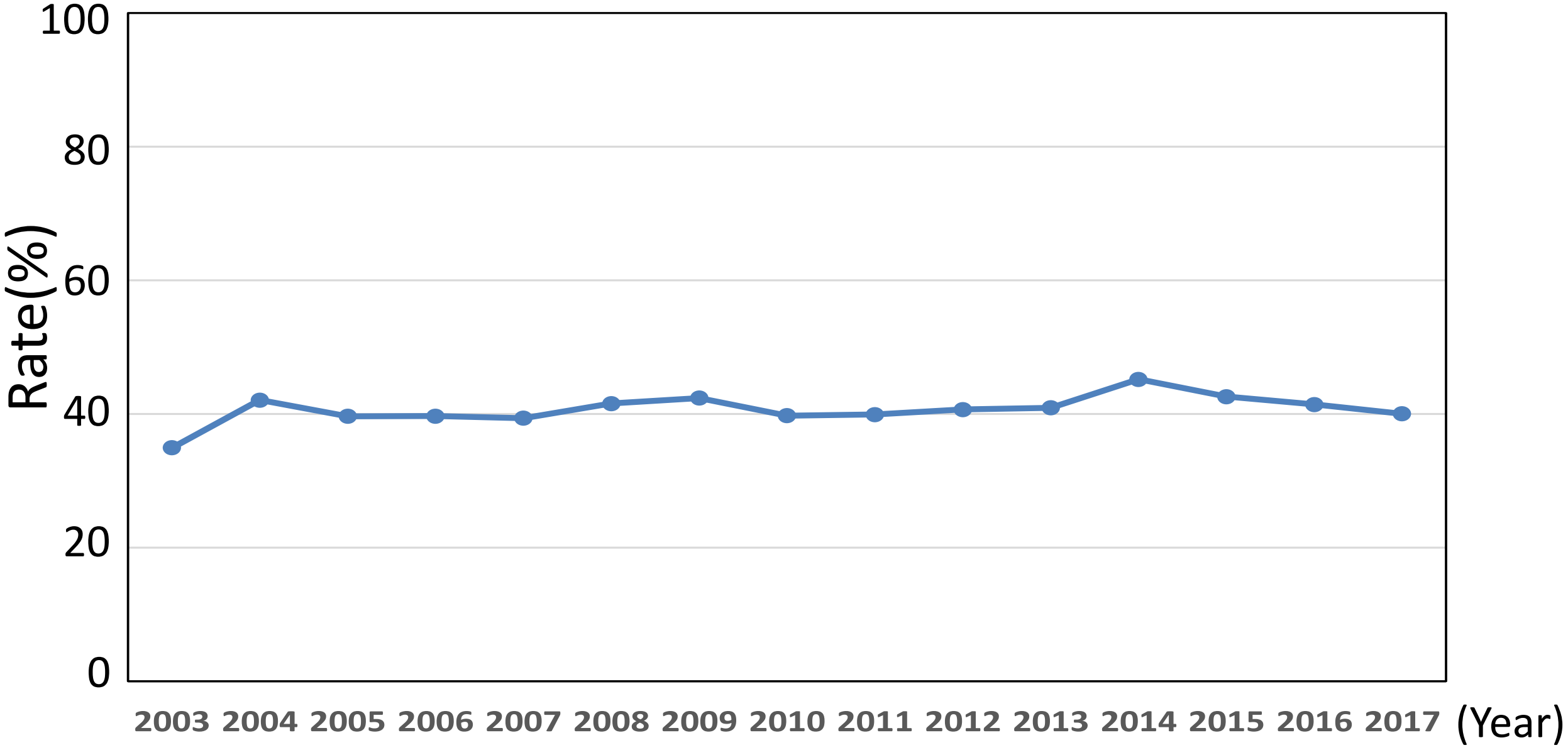
Trends in length of CPAP use



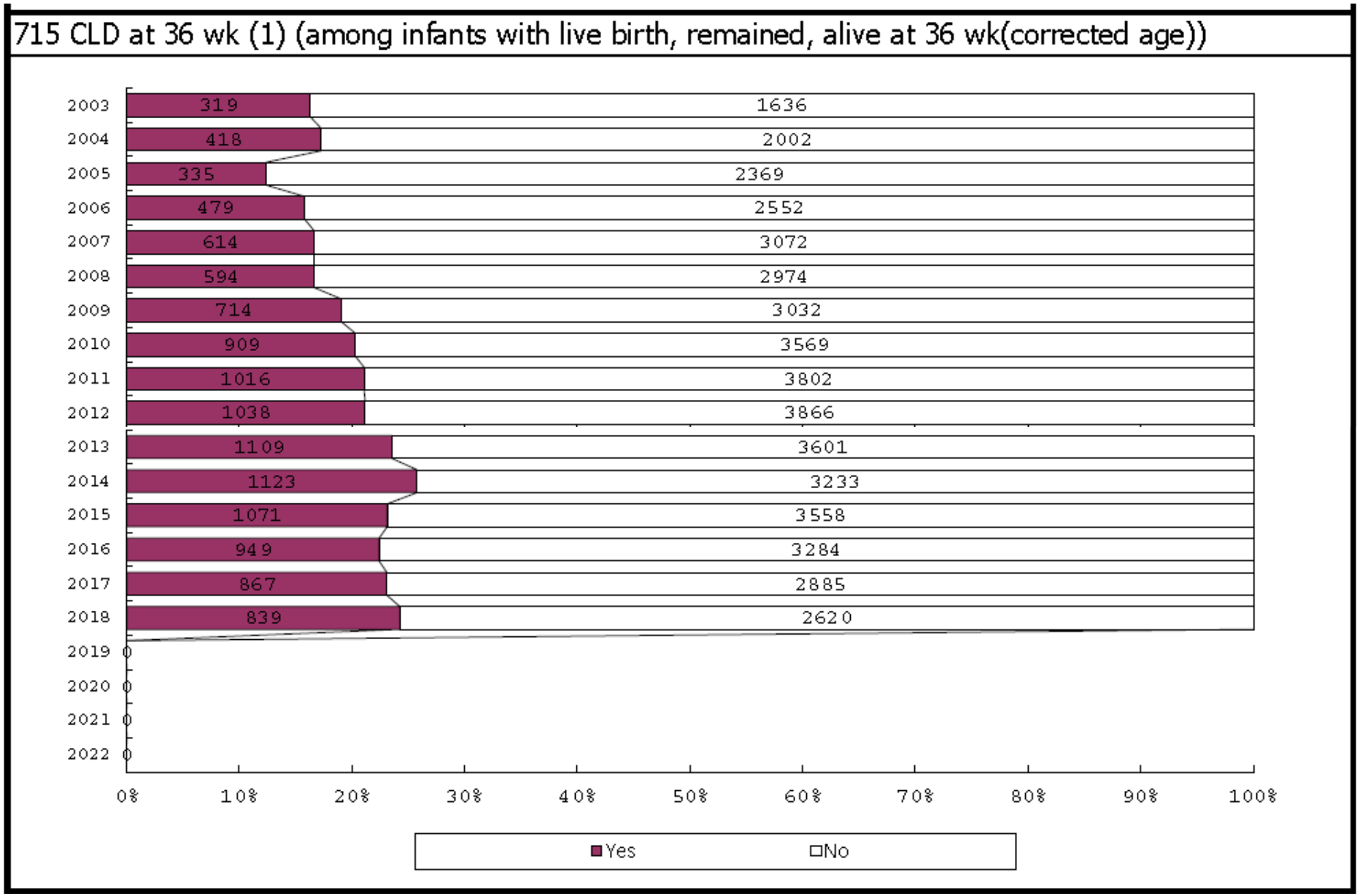
Trends in length of mechanical ventilation



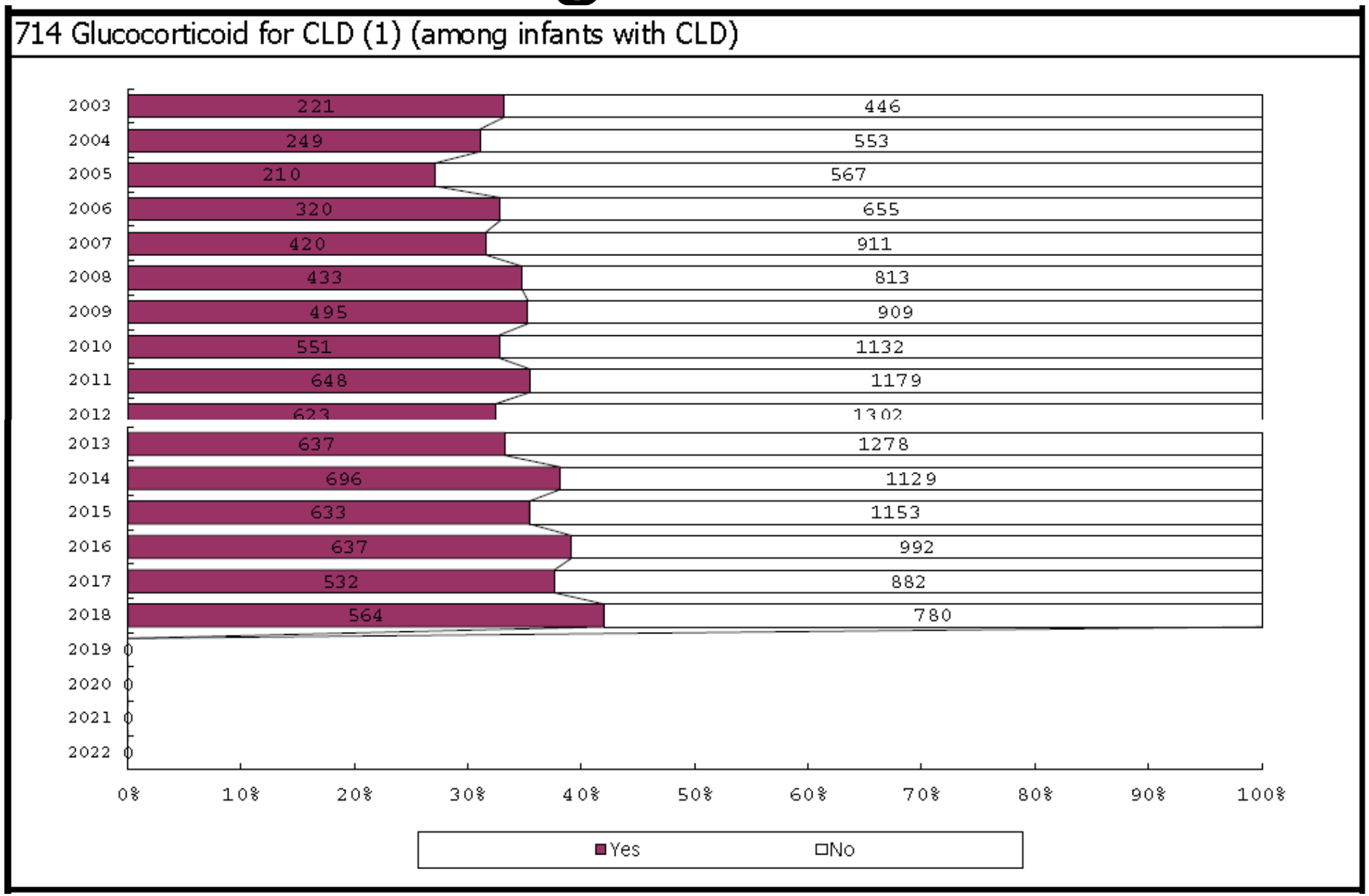
Trends in rates of HFOV use



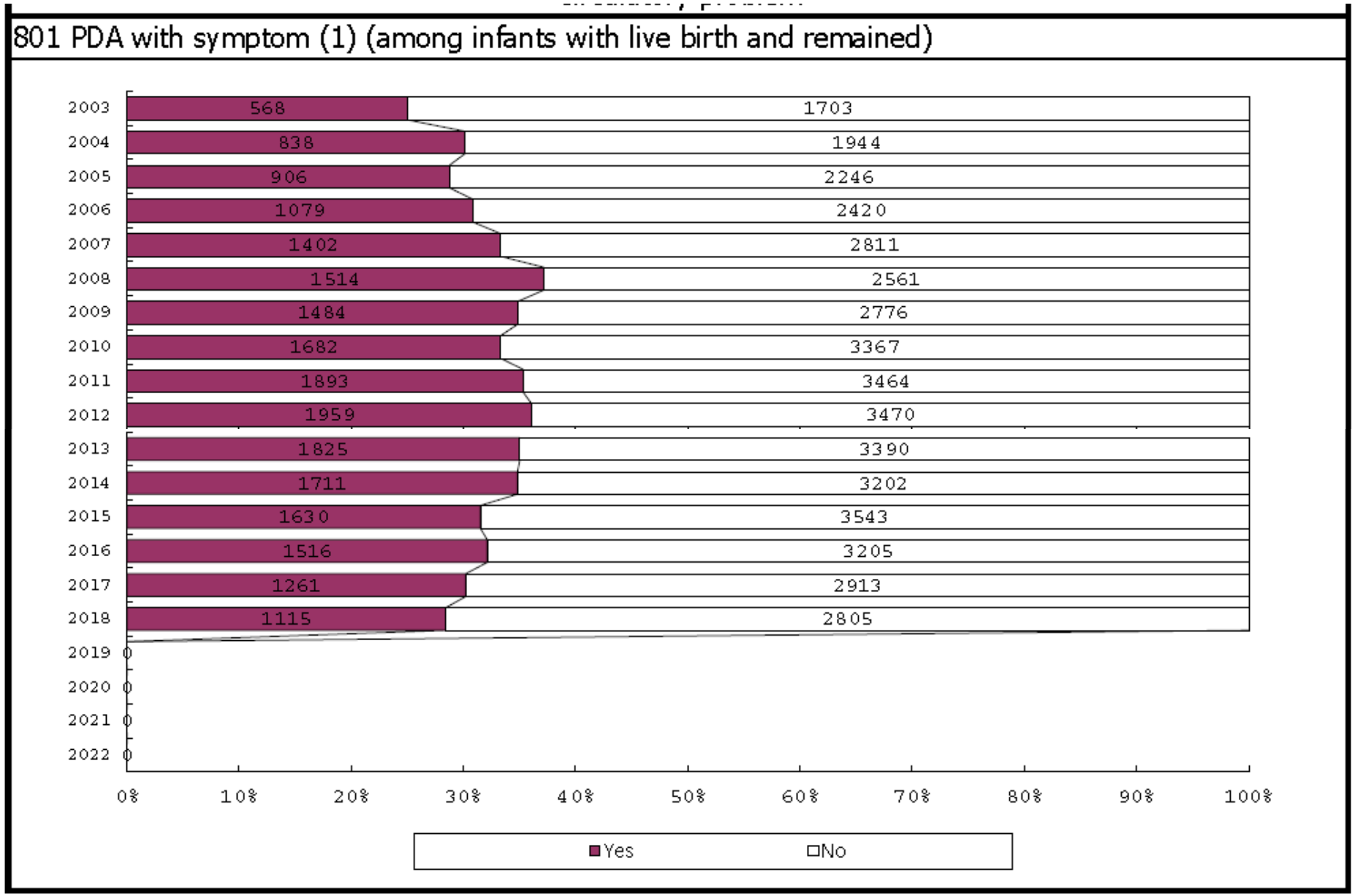
Trends in incidences of CLD at 36 GW



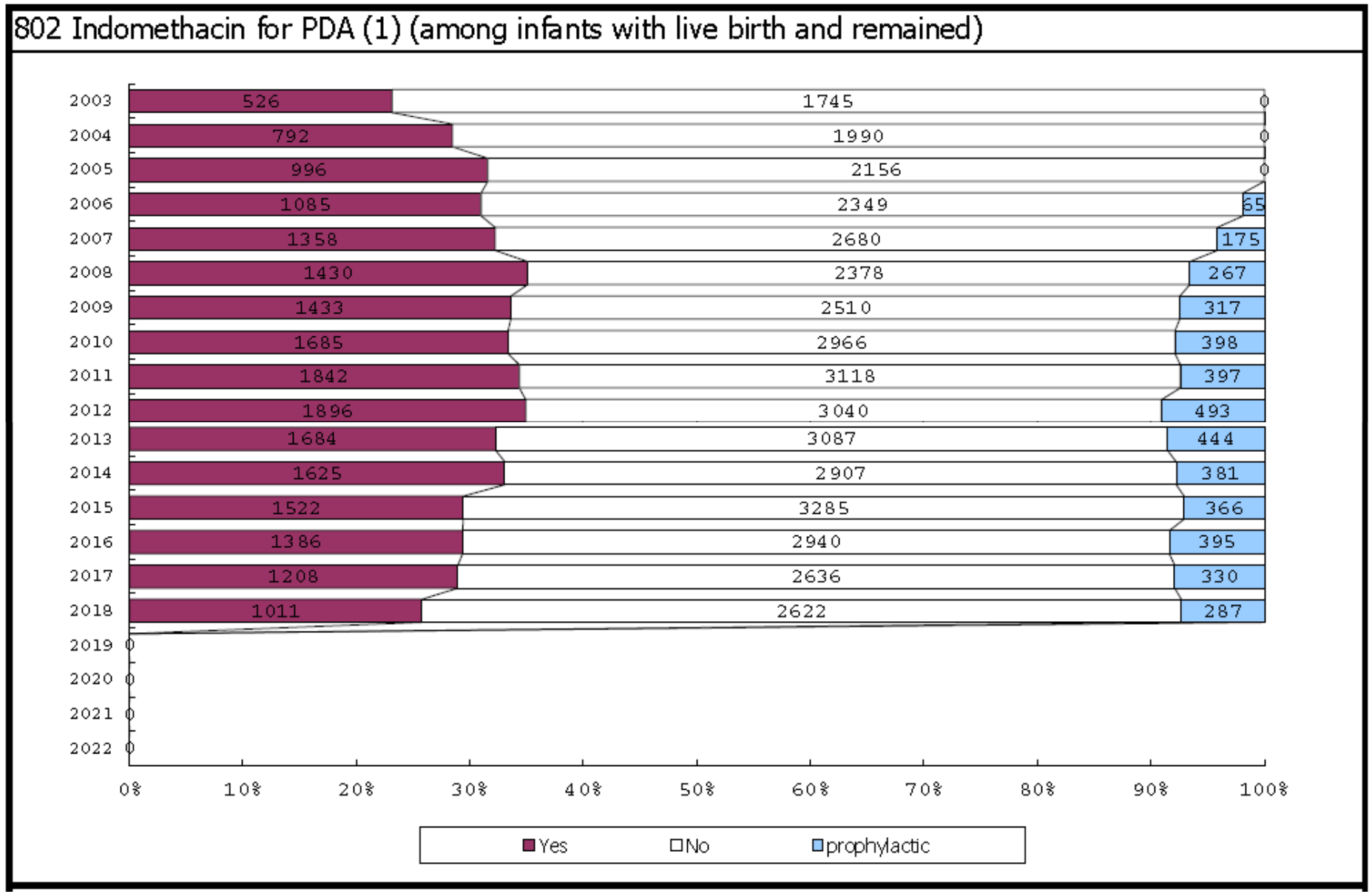
Trends in rates of glucocorticoid use of CLD



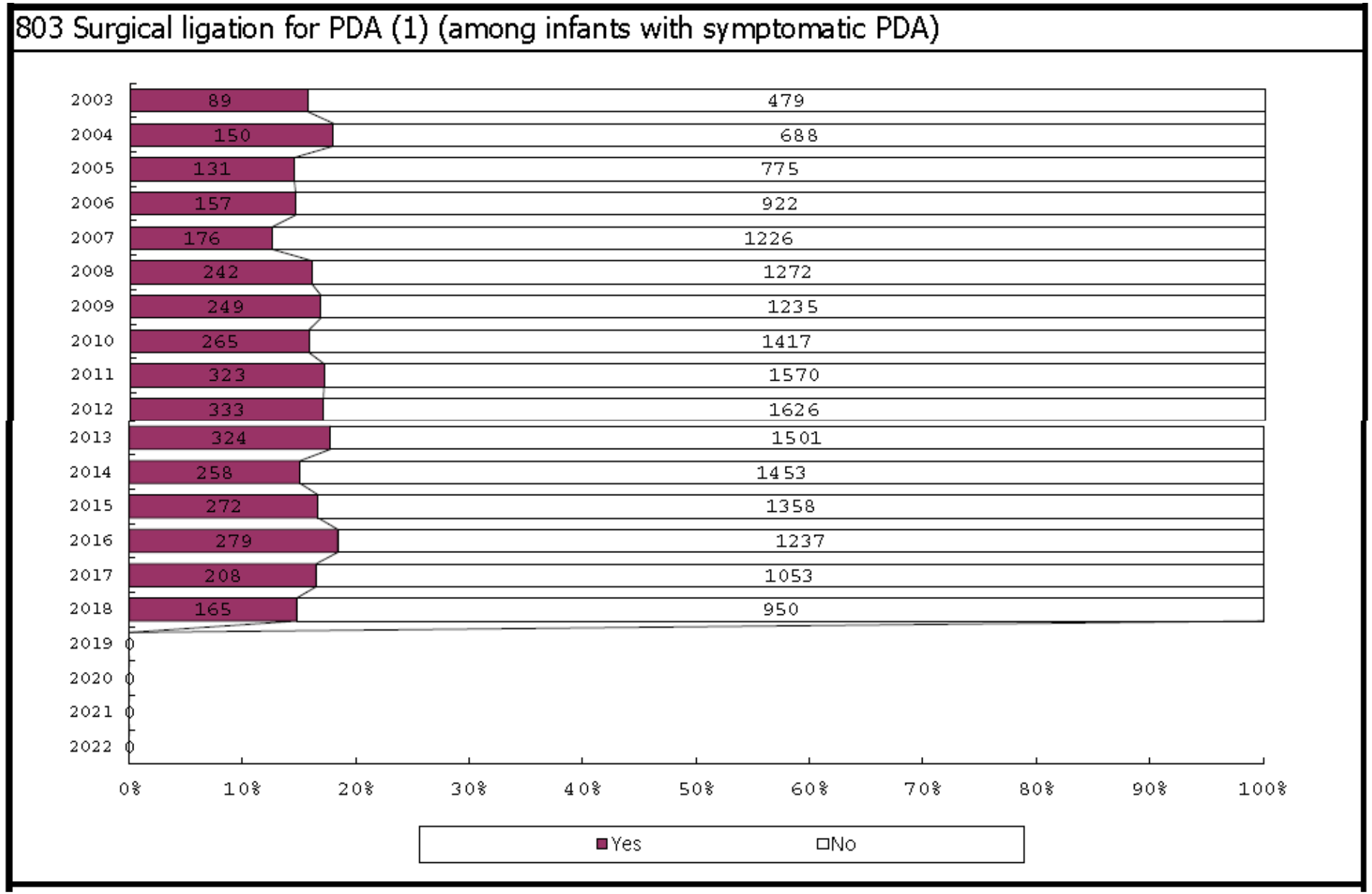
Trends in incidences of PDA



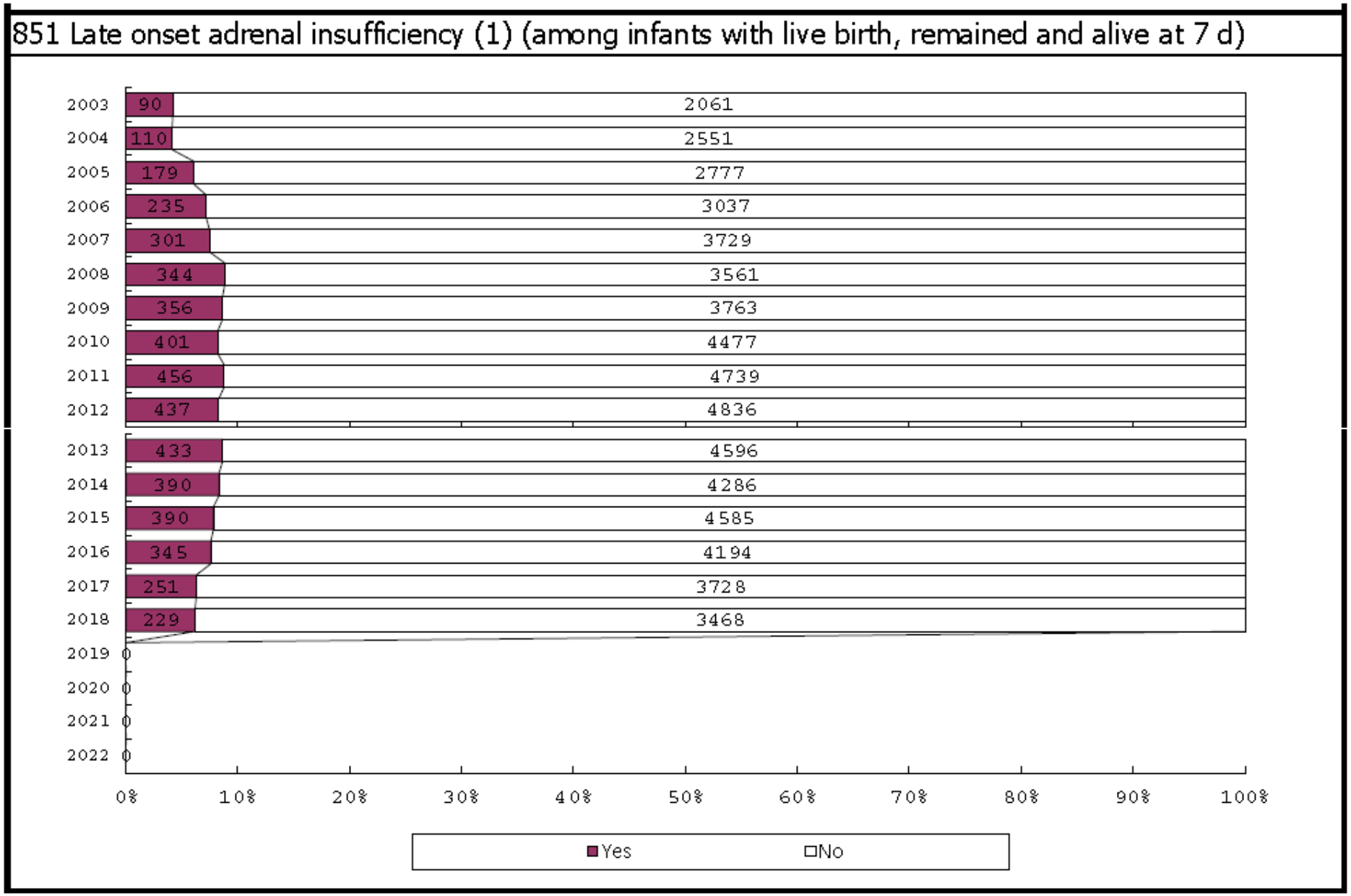
Trends in uses of indomethacin



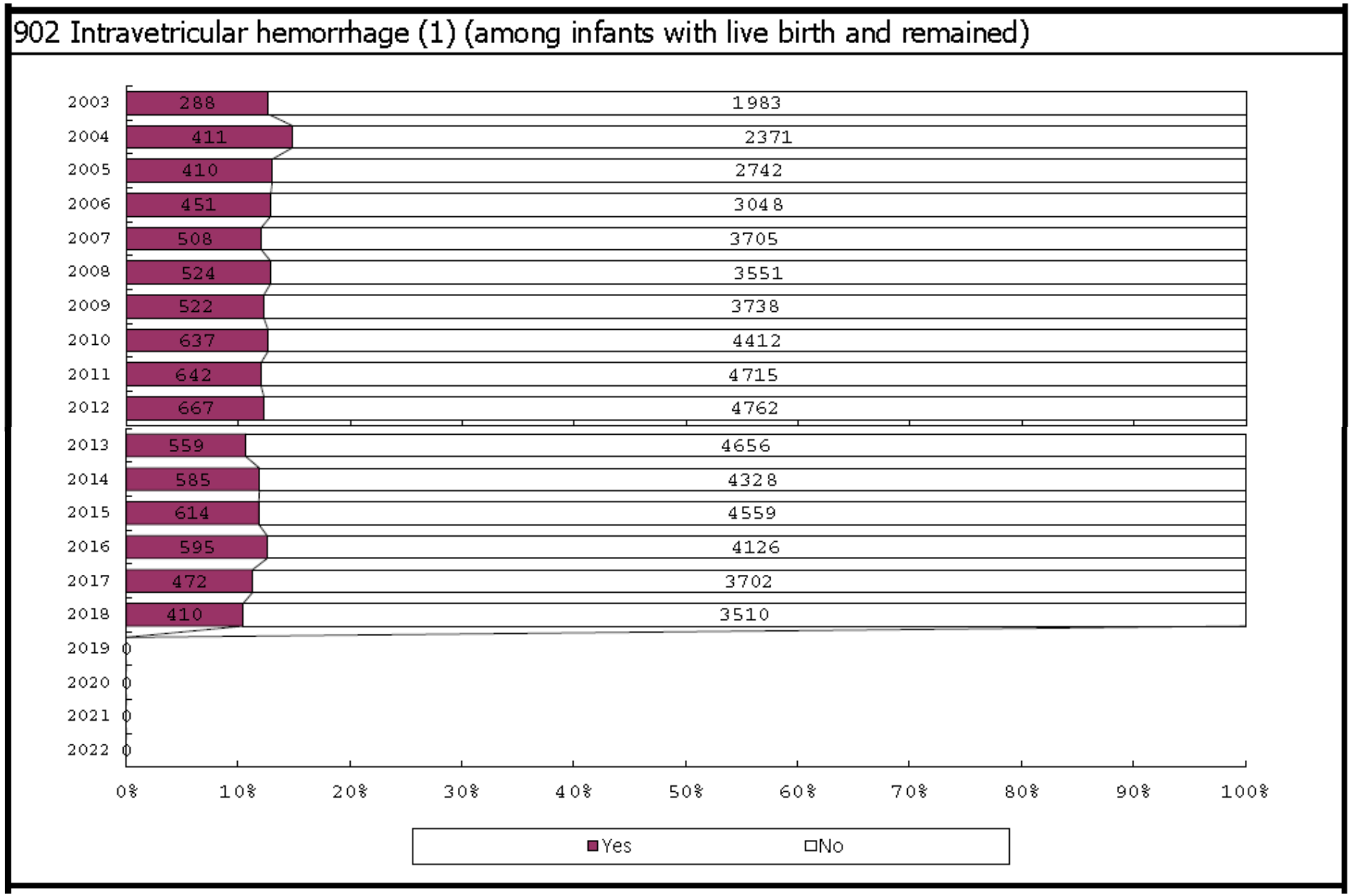
Trends in rates of PDA ligation



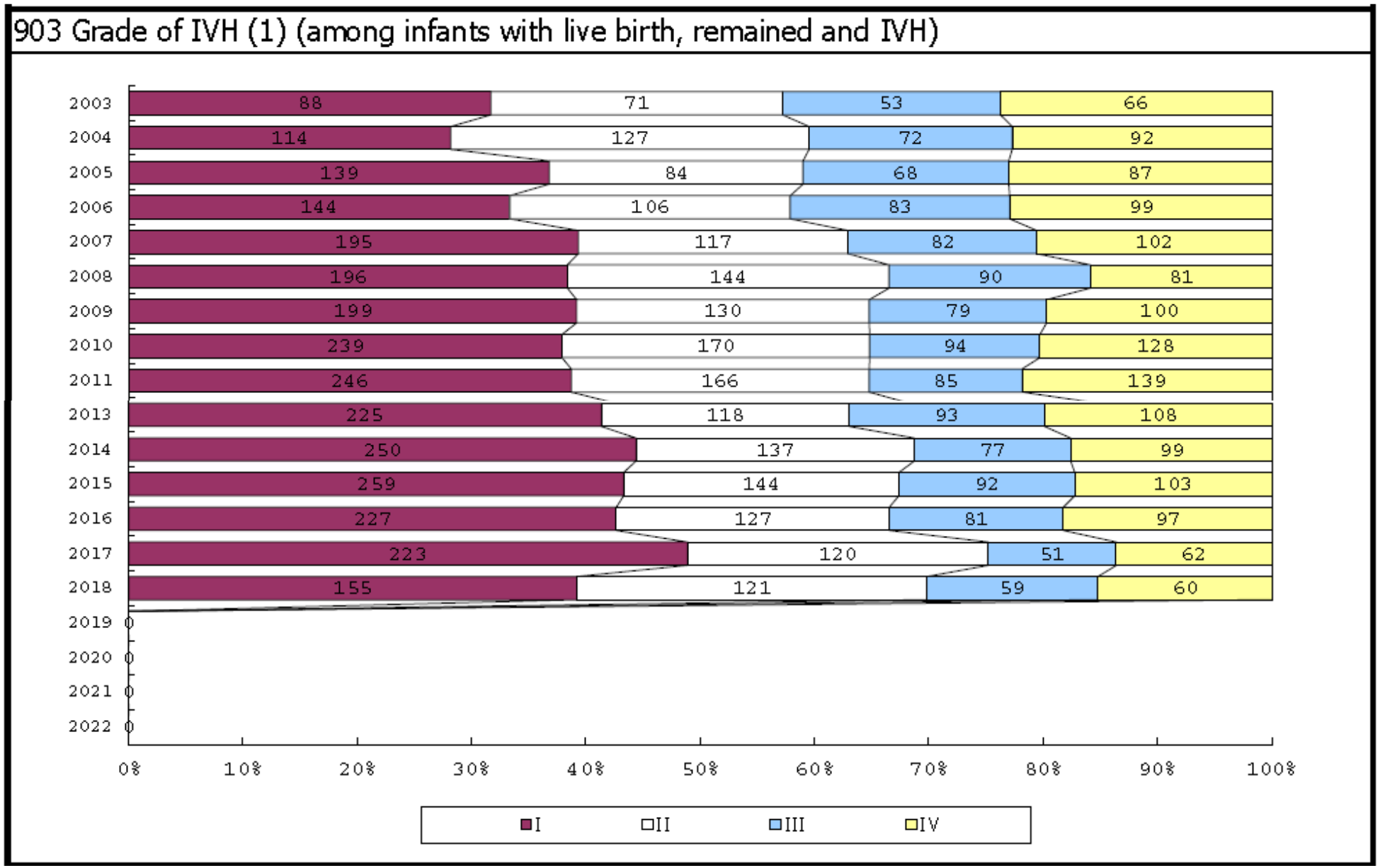
Trends in rates of late onset adrenal insufficiency



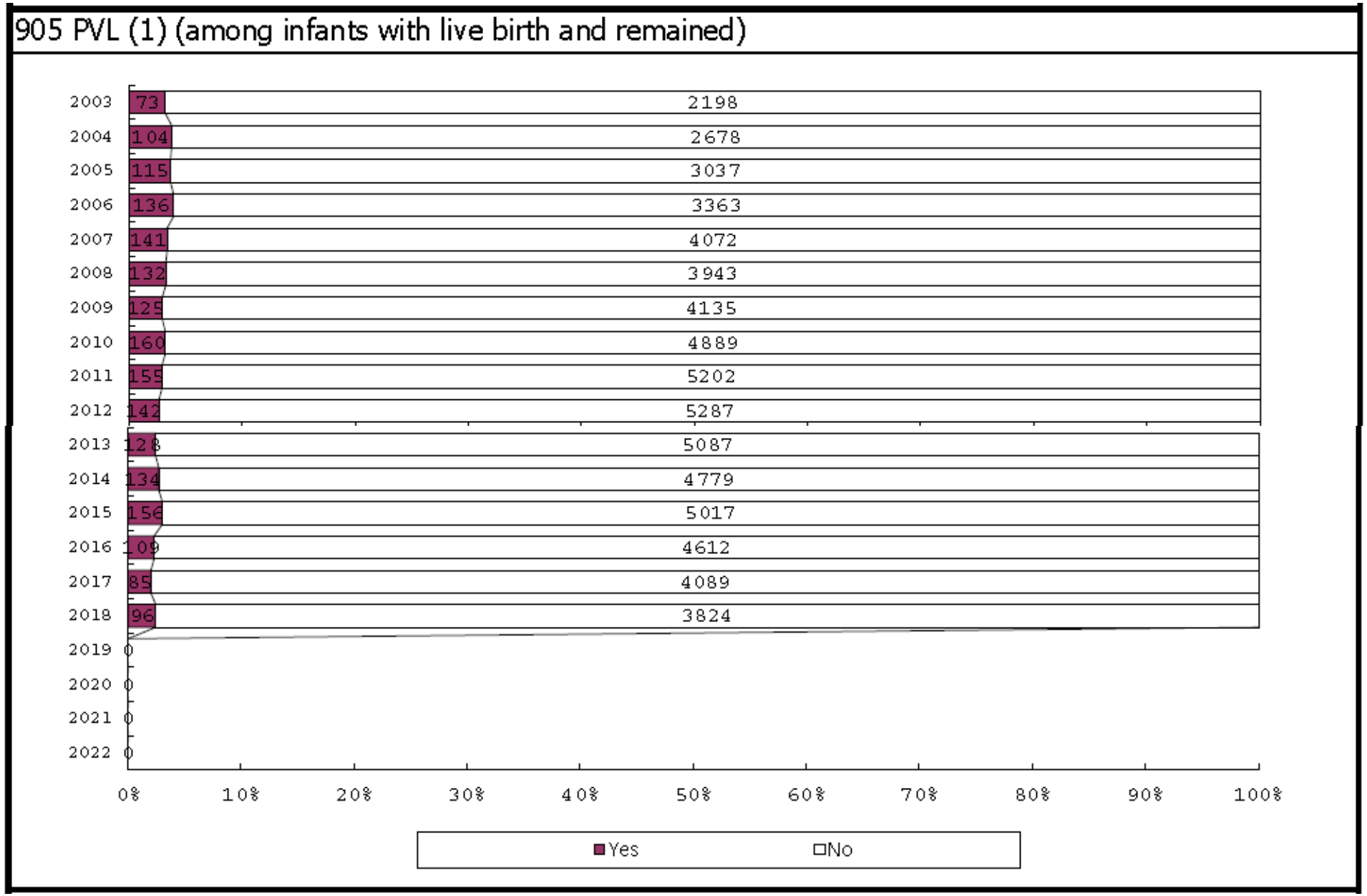
Trends in incidences of IVH



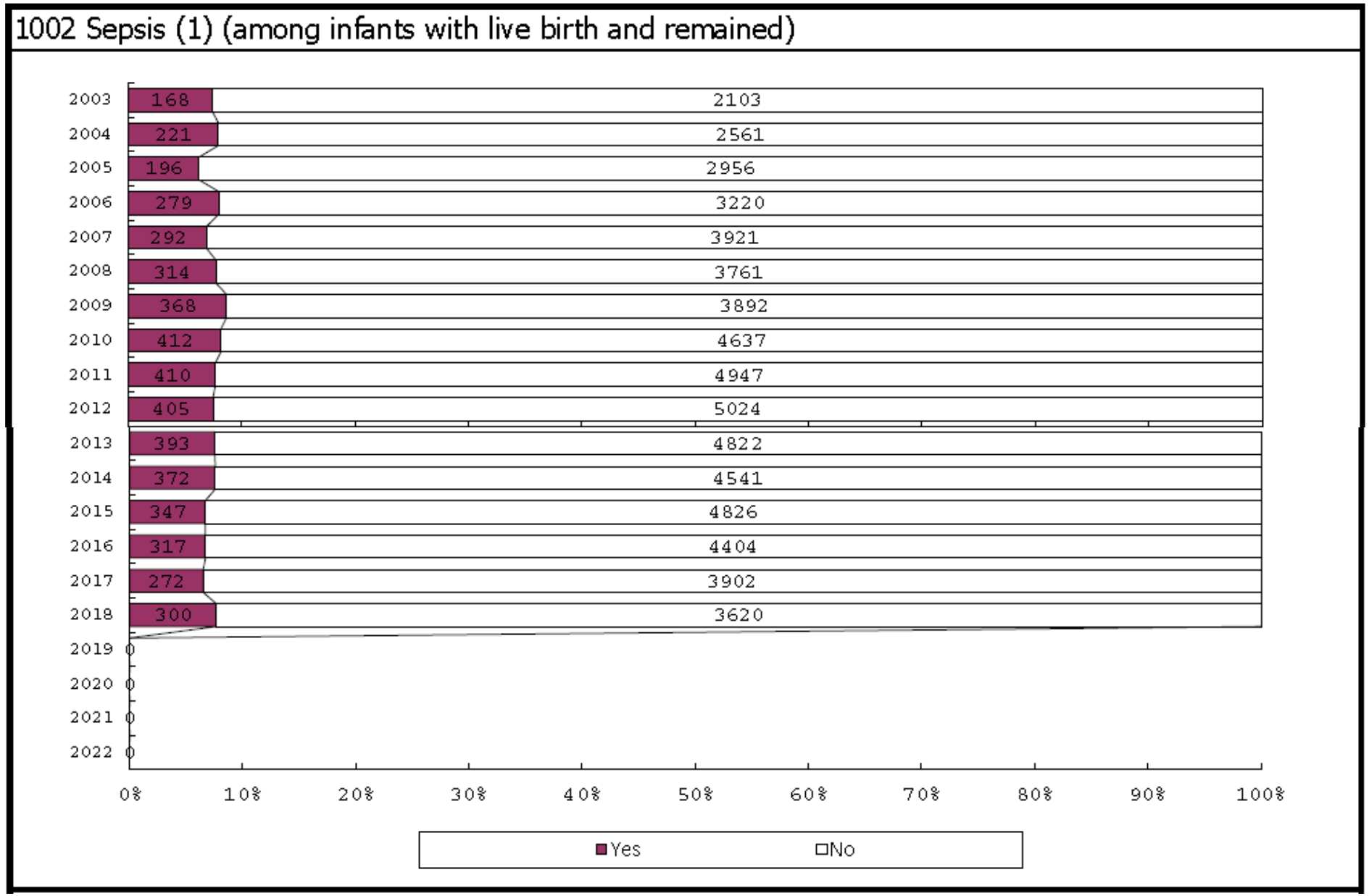
Trends in grades of IVH



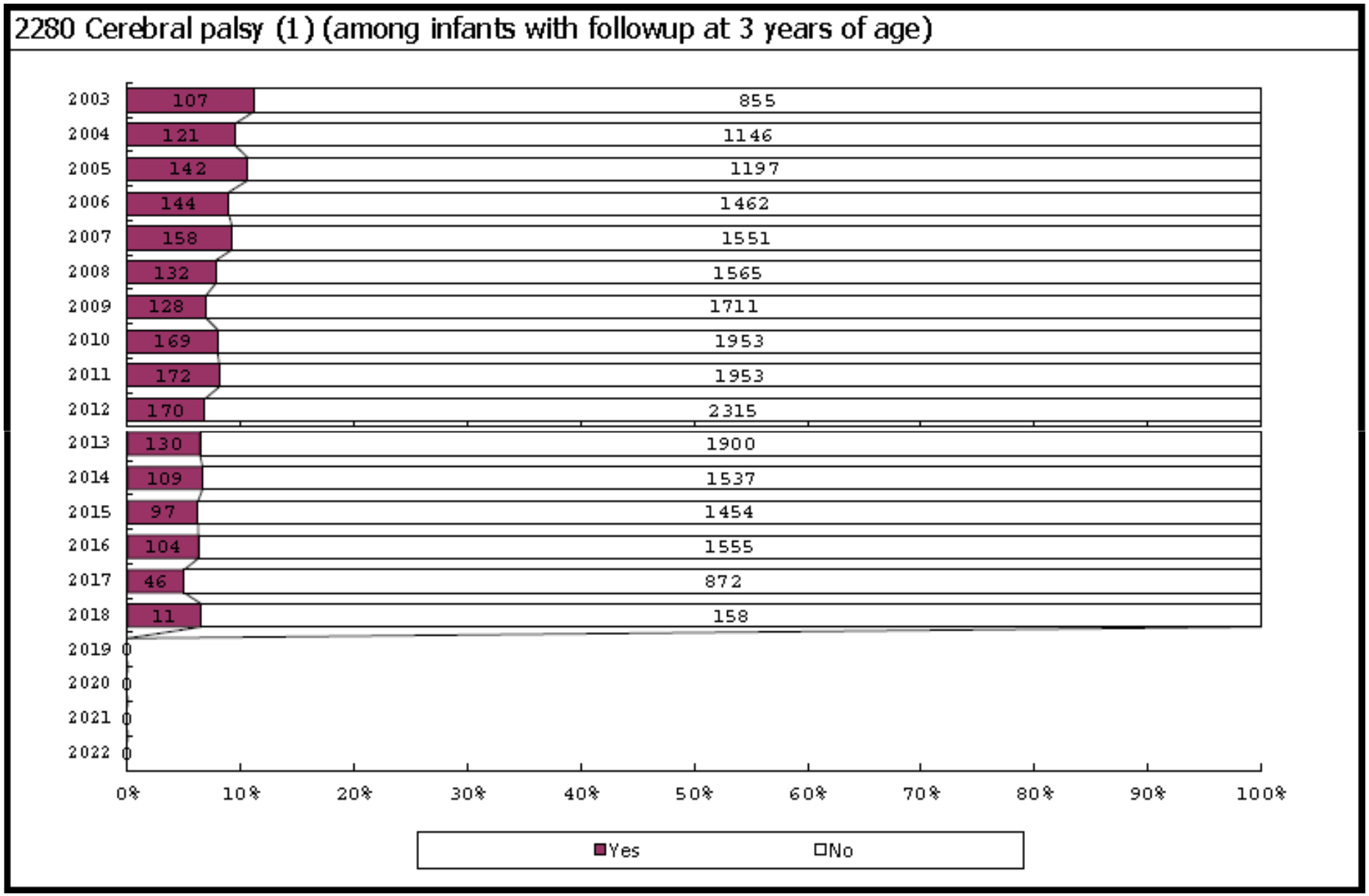
Trends in incidences of PVL



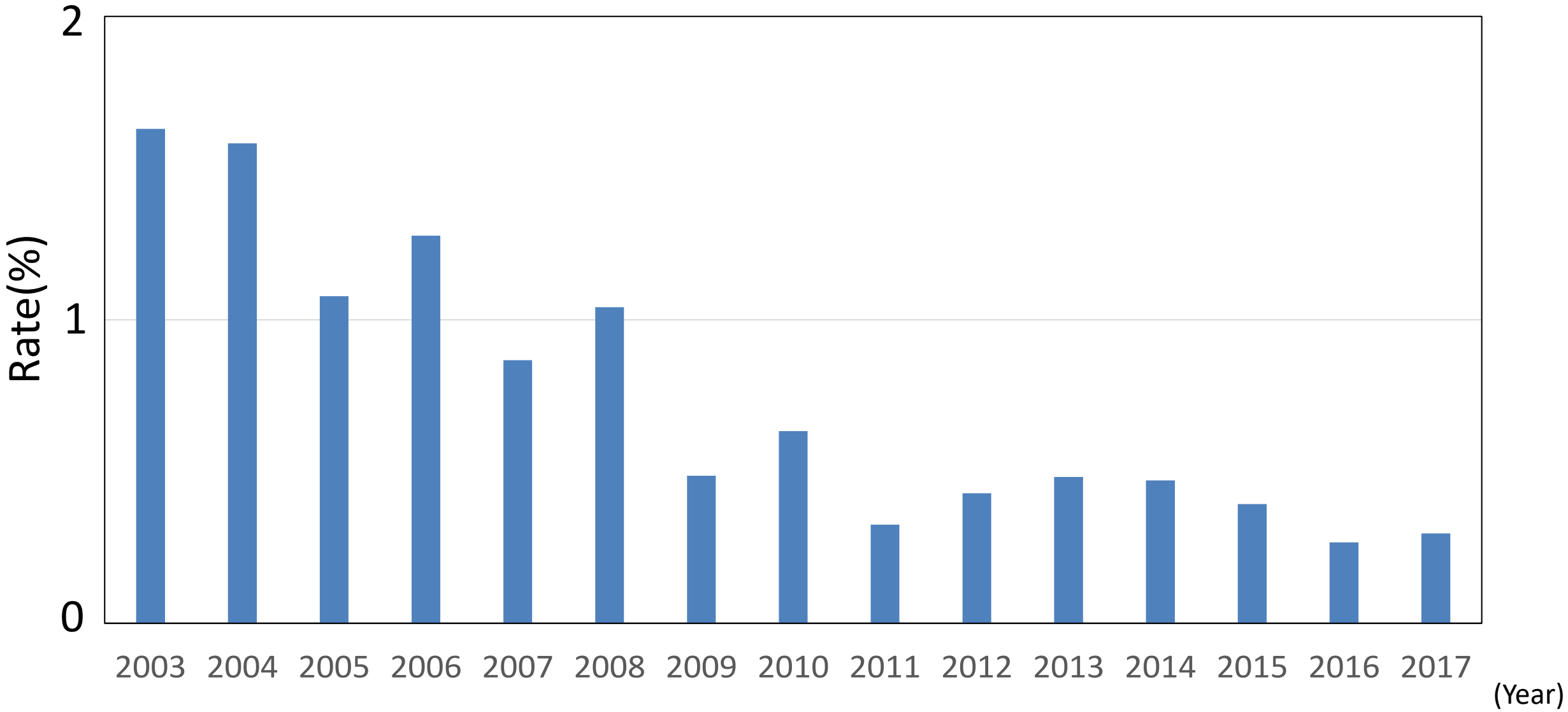
Trends in incidences of sepsis



Trends in incidences of CP at 3 years of age



Trends in incidences of uni- or bi-lateral blindness



Neonatal Intensive Care Manual for the infants born at less than 28 weeks of gestation

- 10 contributors
- 7 chapters, 103 pages
  - Introduction
  - Resuscitation
  - Respiratory support
  - Circulatory support
  - Intravenous fluid management
  - Enteral feeding
  - Infection control
  - NICU environment

Neonatal Intensive Care Manual for the infants born at less than 28 weeks of gestation

(Ver. 1)

Neonatal Research Network of Japan

(http://plaza.umin.ac.jp/nrndata/)

Contributors (according to writing order)

Satoshi Kusuda	Kyorin University
Tetsuya Isayama	National Center for Child Health and Devel
Shinya Hirano	Osaka Women's and Children's Hospital
Hidehiko Nakanishi	Kitasato University
Tomohiko Nakamura	Nagano Children's Hospital
Hiroko Iwami	Osaka City General Hospital
Masahiro Hayakawa	Nagoya University
Isamu Hokuto	St. Marianna Medical University
Tokuo Miyazawa	Showa University
Masanori Fujimura	Osaka Women's and Children's Hospital

(2019 All rights reserved by Neonatal Research Network of Japan)

Summary

- Neonatal Database system operated successfully since 2003
- Continuous improvement in mortality and morbidities
- However, some morbidities still remain high
- Need continuous efforts to improve outcomes among high risk infants
- NICU manual for the infants born at less than 28 weeks of gestation was published, please visit our web site (http://plaza.umin.ac.jp/nrndata/pdf/NICUManual.pdf)

Clinical Trials in Newborn Infants

The Case for URGENT International Collaboration

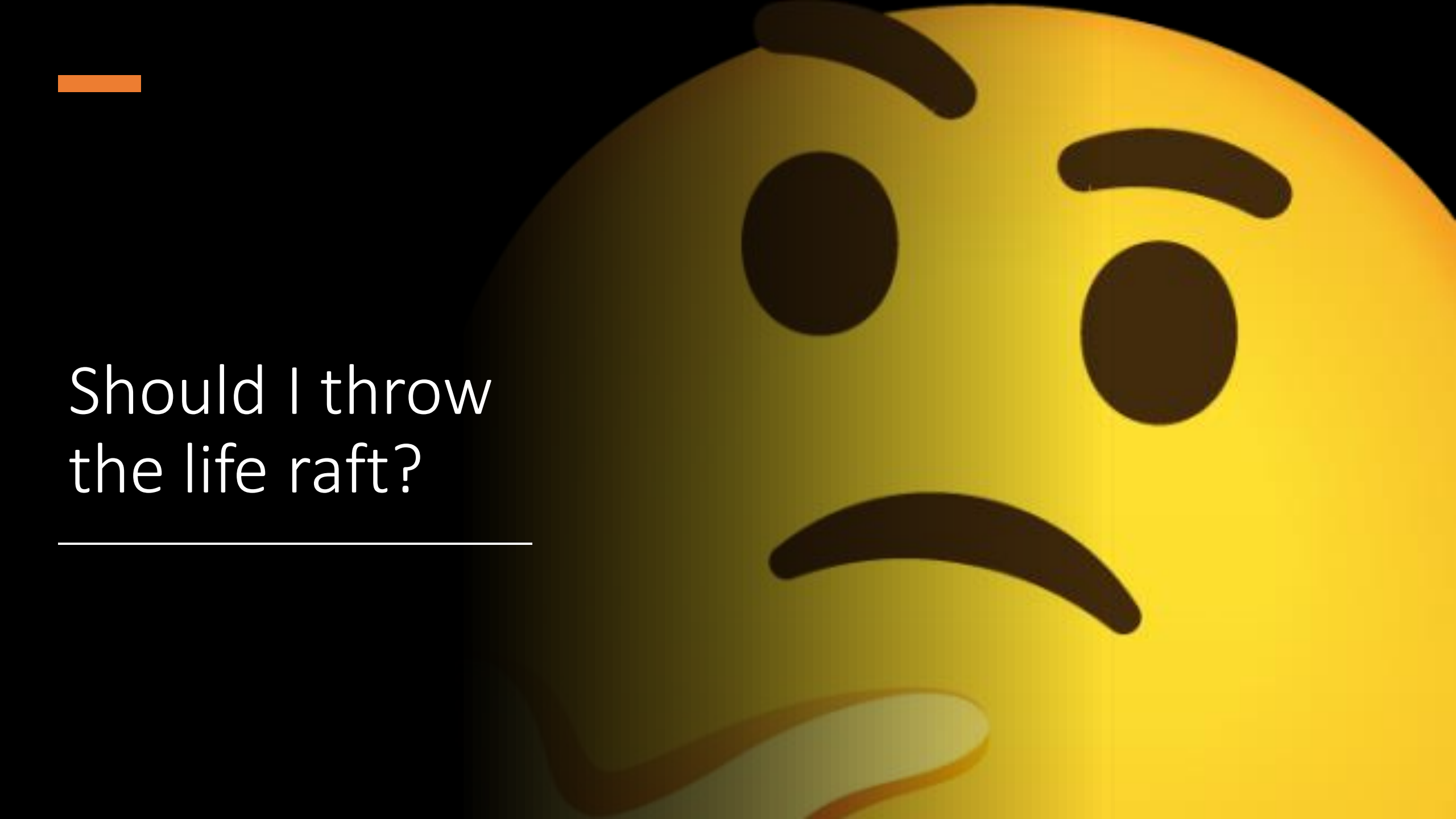
Ju Lee Oei
Neonatologist
Royal Hospital for Women
University of New South Wales
Sydney Australia

Problem: Drowning Man

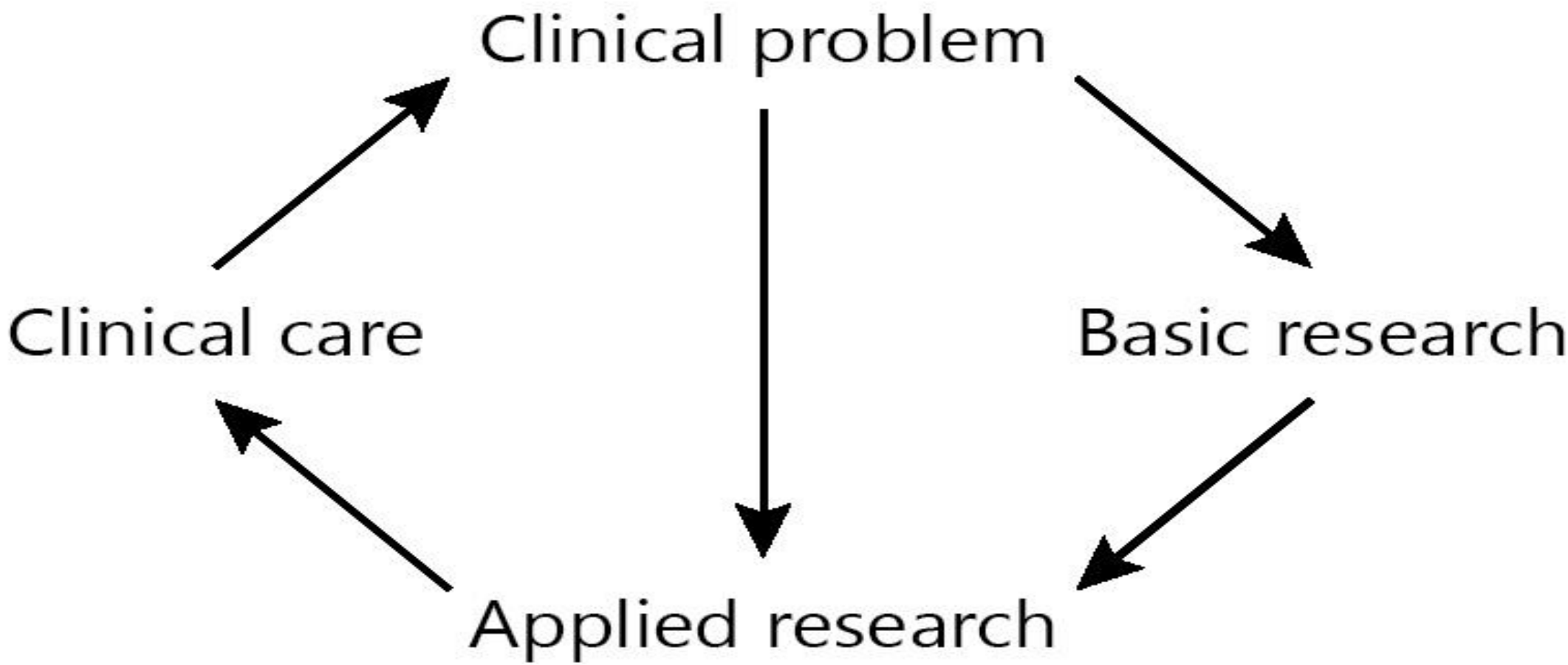
Question: How to save him?

I don’t have any evidence that a life raft will save him

Should I throw the life raft?



Framework for solving clinical problems



This will take years and babies do not have time to waste

Trials Improve Health

- Polio vaccines = eradication of polio
- Childhood cancer survival: 28% in 1960's to 79% to 2005 to >80% today
- Inclusion effect (Lantos 1999)
  - Just being part of a study will improve outcomes

Ian Chalmers, Founder of Cochrane
Medical Emergency Card
Invite me to participate in all randomized controlled trials for which I am potentially eligible

Antenatal Steroids

A demonstration of slow uptake of a lifesaving intervention

- #1 most important intervention in neonatology
- 1969 – Liggins (obstetrician) + Howie (Neonatologist) in New Zealand randomized 282 women to antenatal steroids
- Rejected by Lancet (not interesting)
- Published by Pediatrics in 1972
- Findings
  - Reduced early neonatal mortality 15% to 3%
  - RDS reduce 26% to 9%
- Recruitment continued to **1974** total 1142 women + 1248 babies

How much more evidence do we need?

1st systematic review of ANS (Crowley)

- 12 trials
- Showed that ANS reduced death, IVH, NEC without increasing infection

1981

1992

ANS meta-analysis figure adopted as image for Cochrane collaboration to show that faster uptake could have prevented the deaths of thousands of babies

Robert & Dalziel – 21 studies (3885 women + 4269 infants) concluded "A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions"

2006

Antenatal Steroids Have Varied Uptake

1980s

Australia and New Zealand – **almost all** eligible women received ANS

10-20% take up in USA and UK

1990s

2007-2010

Japan 49% received ANS but mortality lowest (5%) out of 8 neonatal networks


Another Conundrum
Oxygen at Delivery

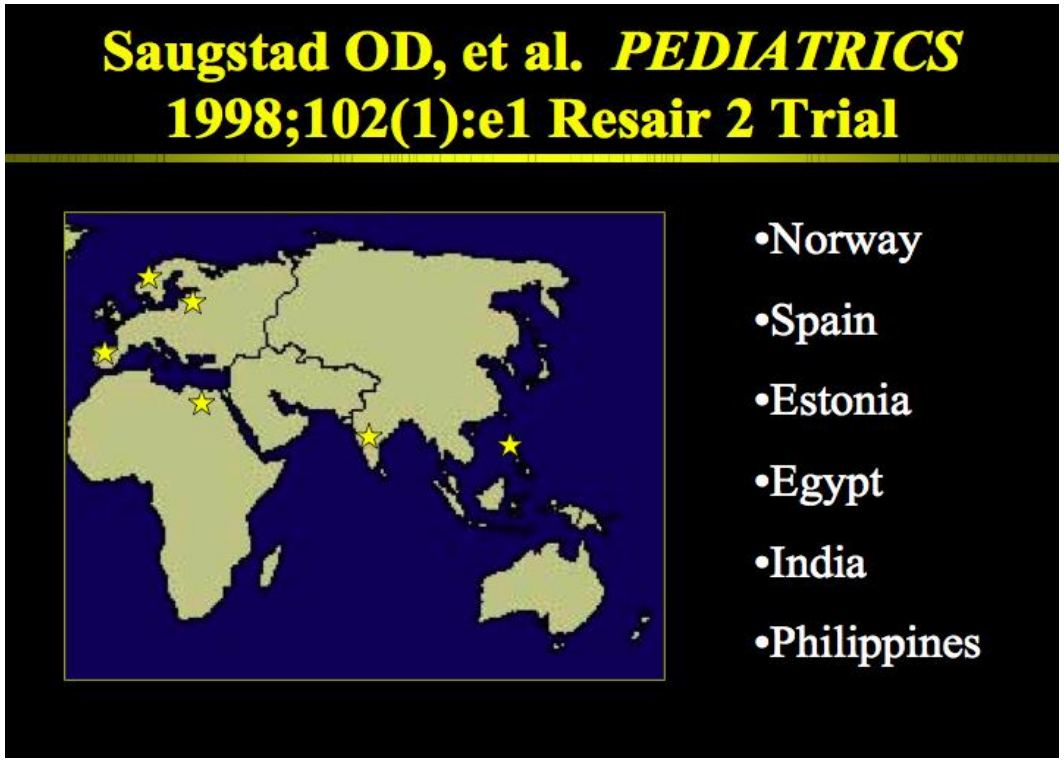
“Oxygen can only be good. Apply liberally”

There was no RCT

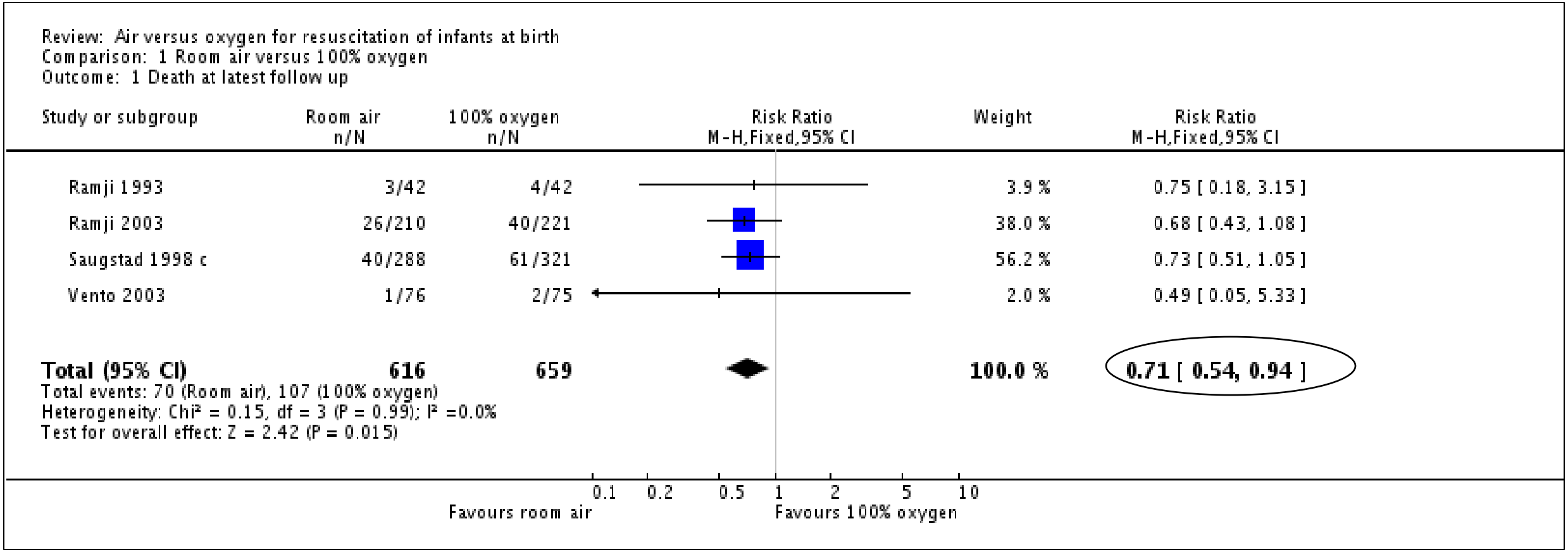
Klaus 1960

The Resair Studies Showed That O_2 May Not Even be Needed for Term Infants

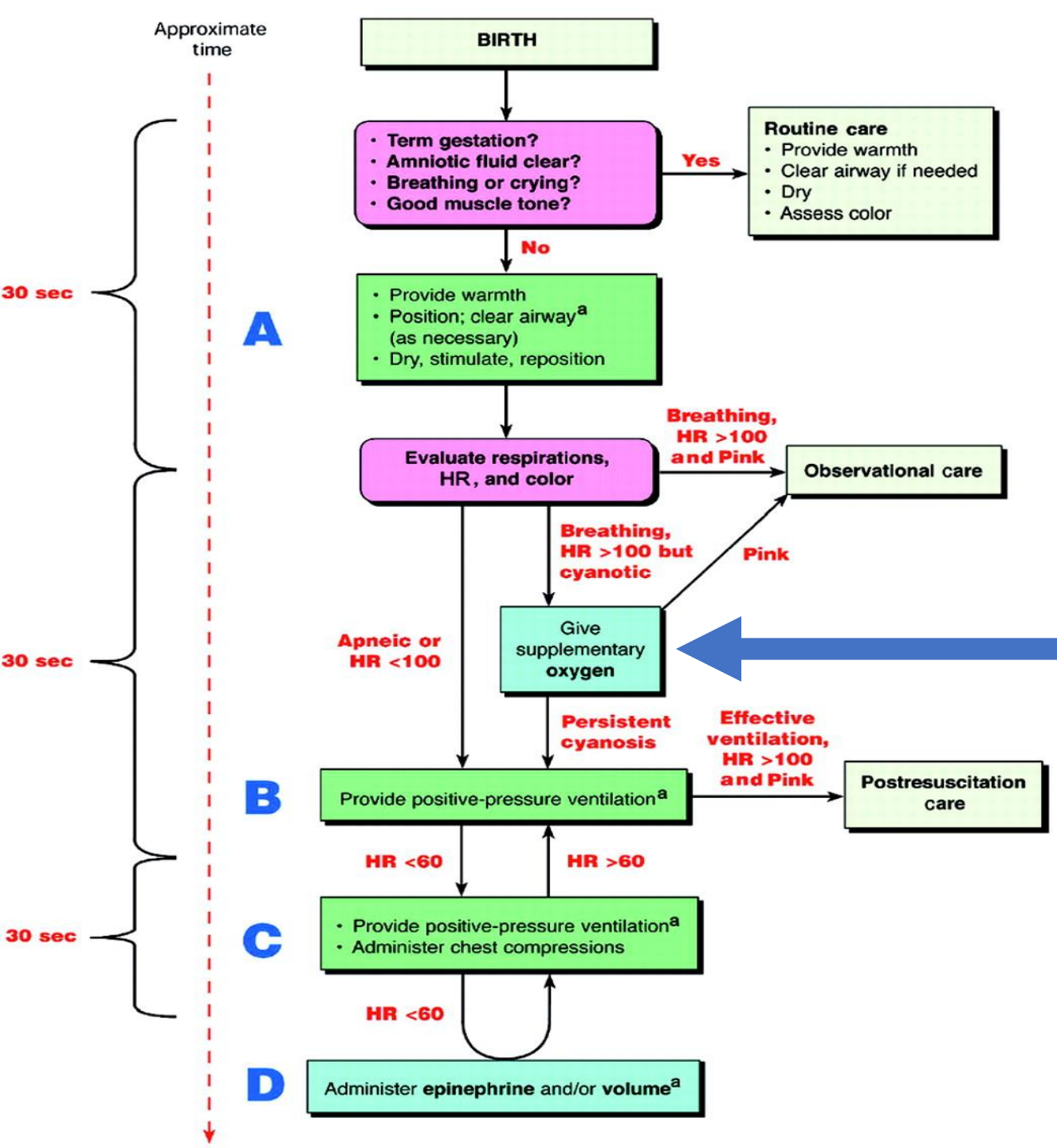
- First to randomize **term/near term** hypoxic infants to either air or 100% O_2 for delivery room resuscitation



Air Decreased Risk of Death by 30%



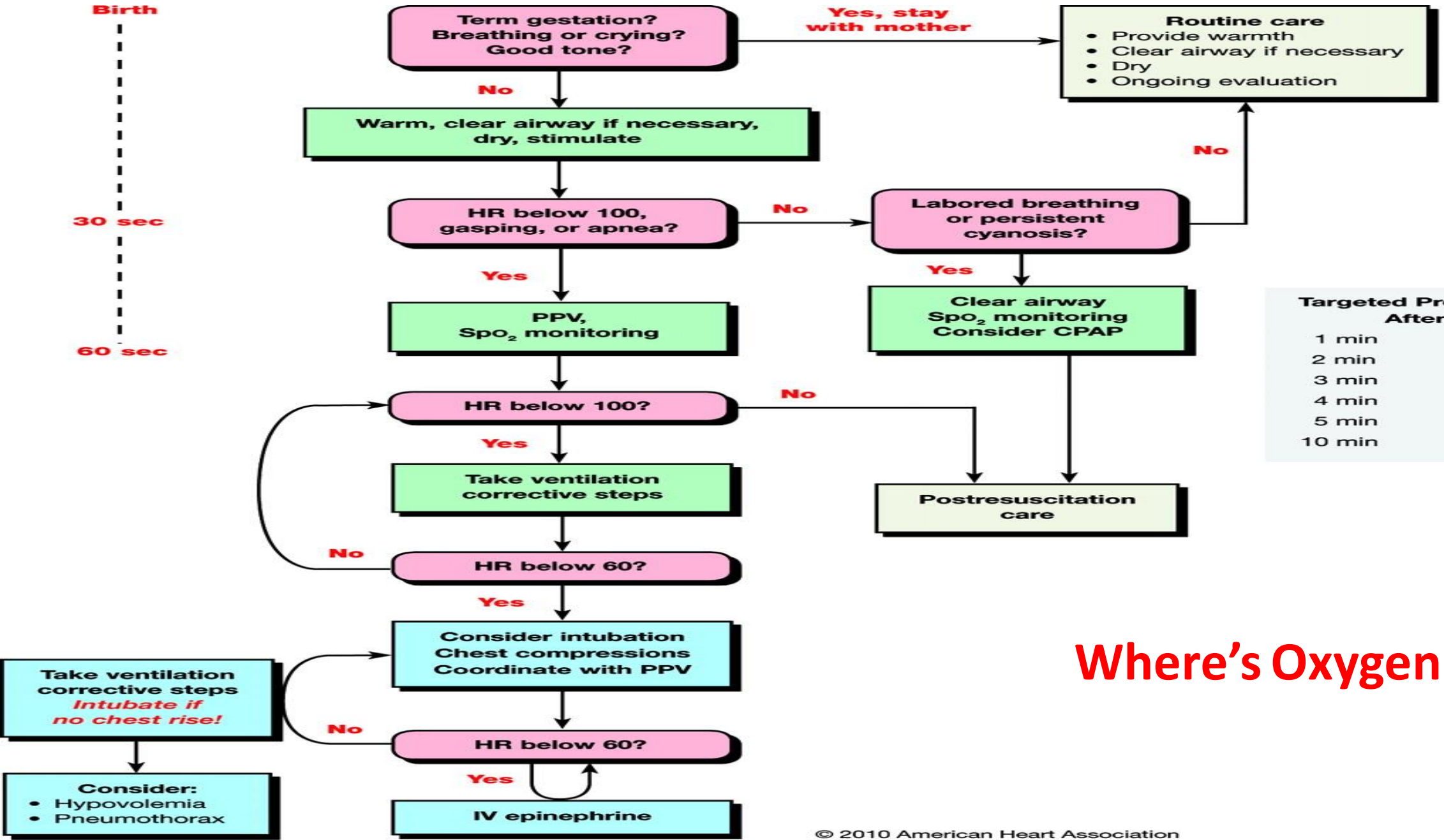
Tan et al 2004



AAP Resuscitation Guidelines 2005

- Standard approach to use **100% oxygen** if PPV required
- **<u>Room air could be used but oxygen must be available if no improvement by 90s</u>**
- Oxygen should be used with **caution in premature infants** due to risk of oxidant injury

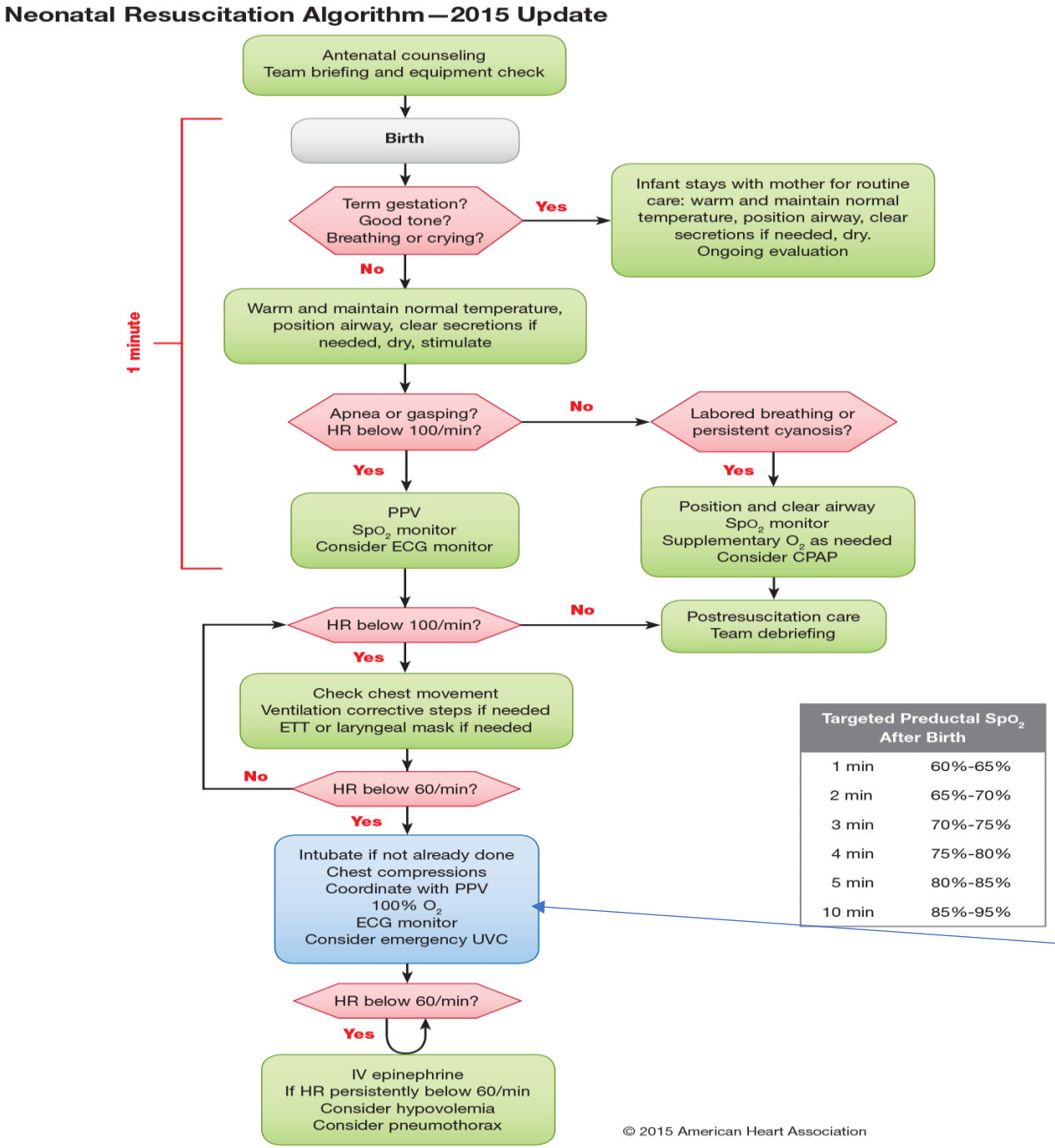
AAP Resuscitation Guidelines 2010



Targeted Preductal Spo_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

Where's Oxygen?

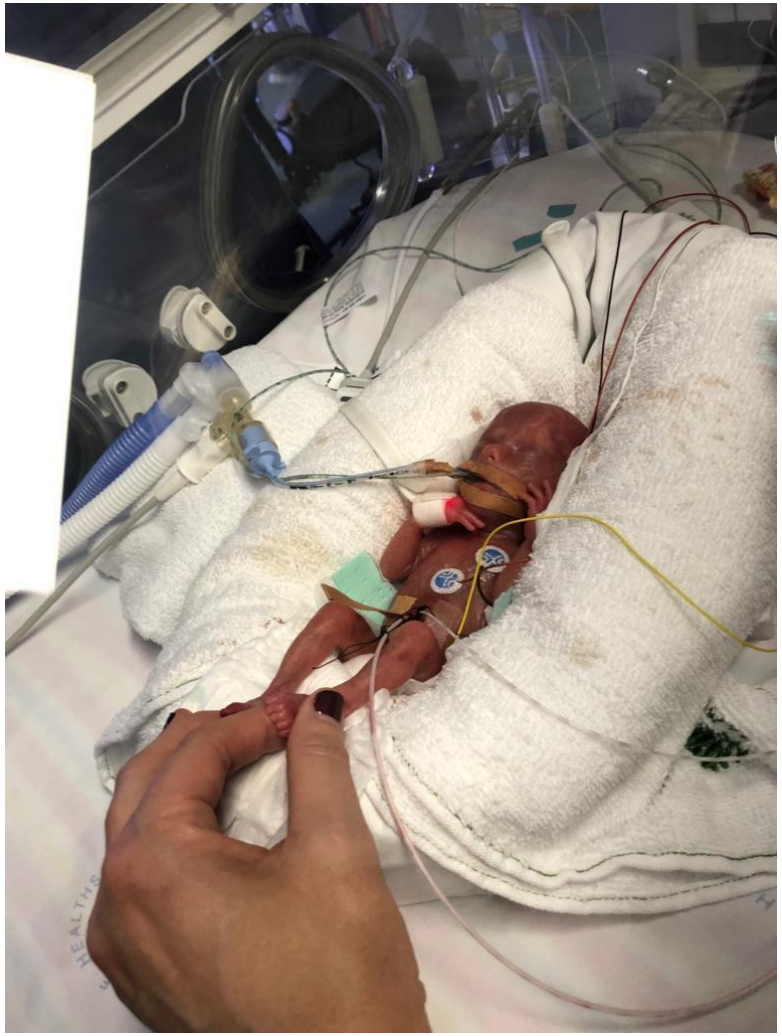
2015 Update to the Resuscitation Guidelines

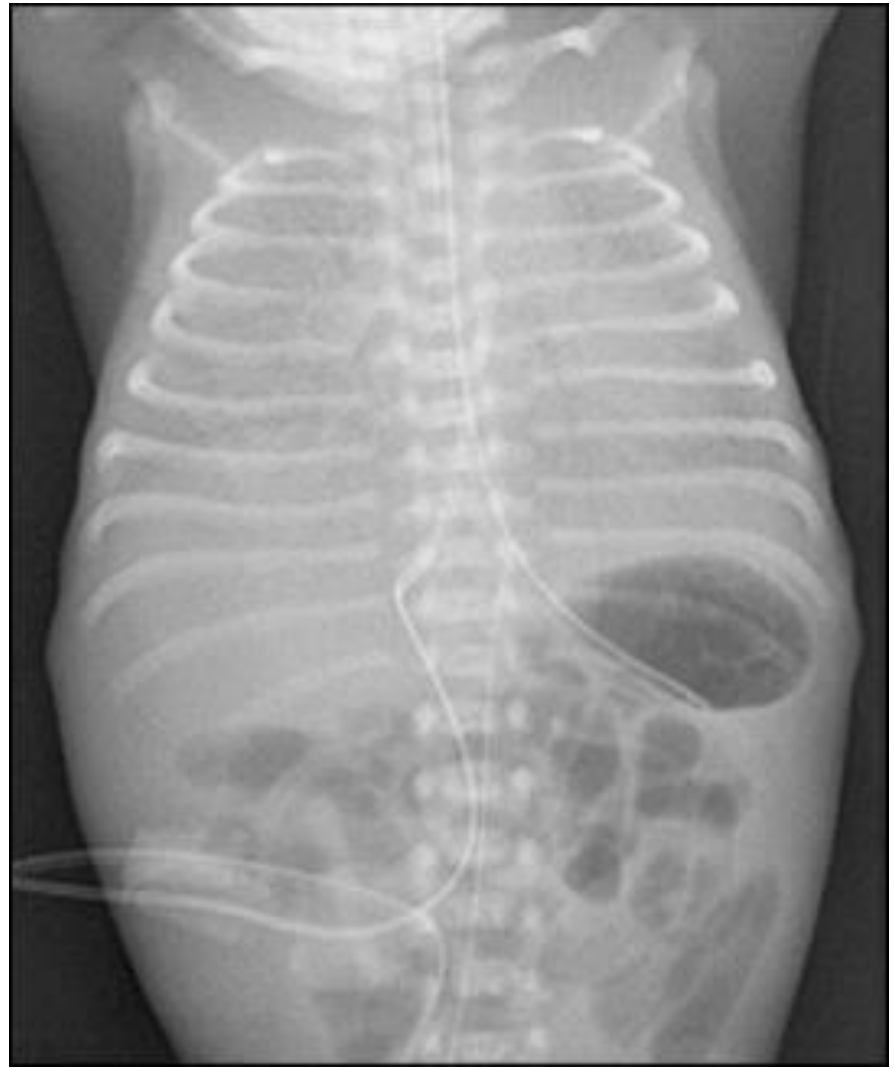


Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

Oxygen's back!

What About the Little Babies?





The To$_2$rpido Study

TO$_2$RPIDO

Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

Ju Lee Oei, MBBS, FRACP, MD,[a,b,c] Ola D. Saugstad, MD, PhD,[d] Kei Lui, MBBS, FRACP, MD,[a,b] Ian M. Wright, MBBS, MRCP, Paeds, FRACP,[e,f,g] John P. Smyth, MBBS, FRACP,[a,b] Paul Craven, MBBS, FRACP,[g] Yueping Alex Wang, BMed, MPH, PhD,[h] Rowena McMullan, MBBS, FRACP,[i] Elisabeth Coates, BSc,[c] Meredith Ward, MBBS, FRACP,[a,b] Parag Mishra, MBBS, FRACP,[a,b] Koert De Waal, MBBS, FRACP, PhD,[g] Javeed Travadi, MBBS, FRACP,[g] Kwee Ching See, MBBS, MRCP,[j] Irene G.S. Cheah, MBBS, MRCP,[k] Chin Theam Lim, MBBS, MRCP,[l] Yao Mun Choo, MBBS, MRCPH,[l] Azanna Ahmad Kamar, MBBS, MRCP,[l] Fook Choe Cheah, MD, FRACP, PhD,[m] Ahmed Masoud, MD,[n] William Tarnow-Mordi, MBBS, MRCP[c]

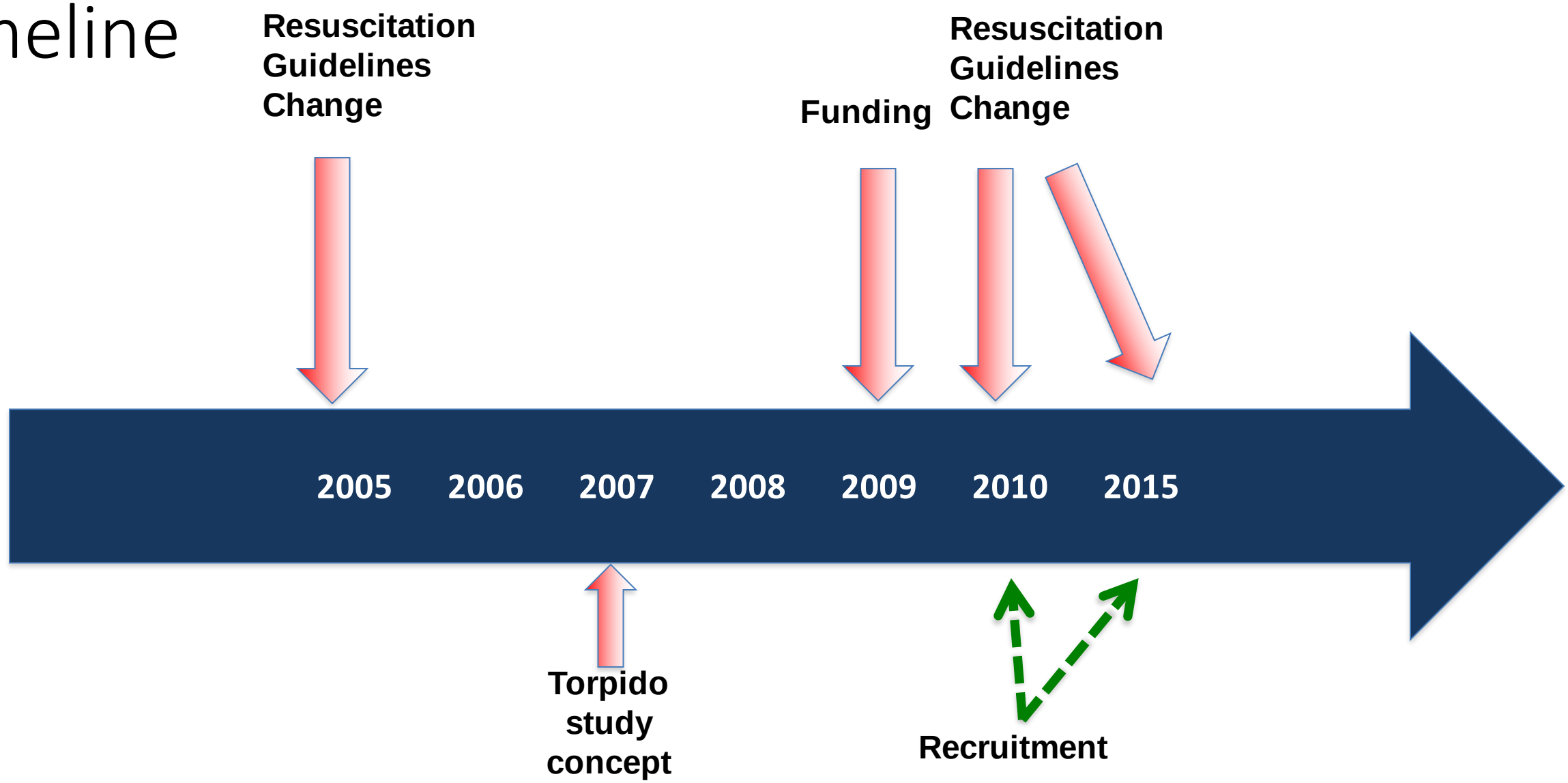
Aim

- To determine if initial FiO_2 0.21 can reduce death and/or major disability at 2 years compared to FiO_2 1.0 in infants <32 weeks gestation

Sample Size

- 988 infants in each arm were required
- To show a 20% reduction in the relative risk of death and major disability at 2 years

Timeline

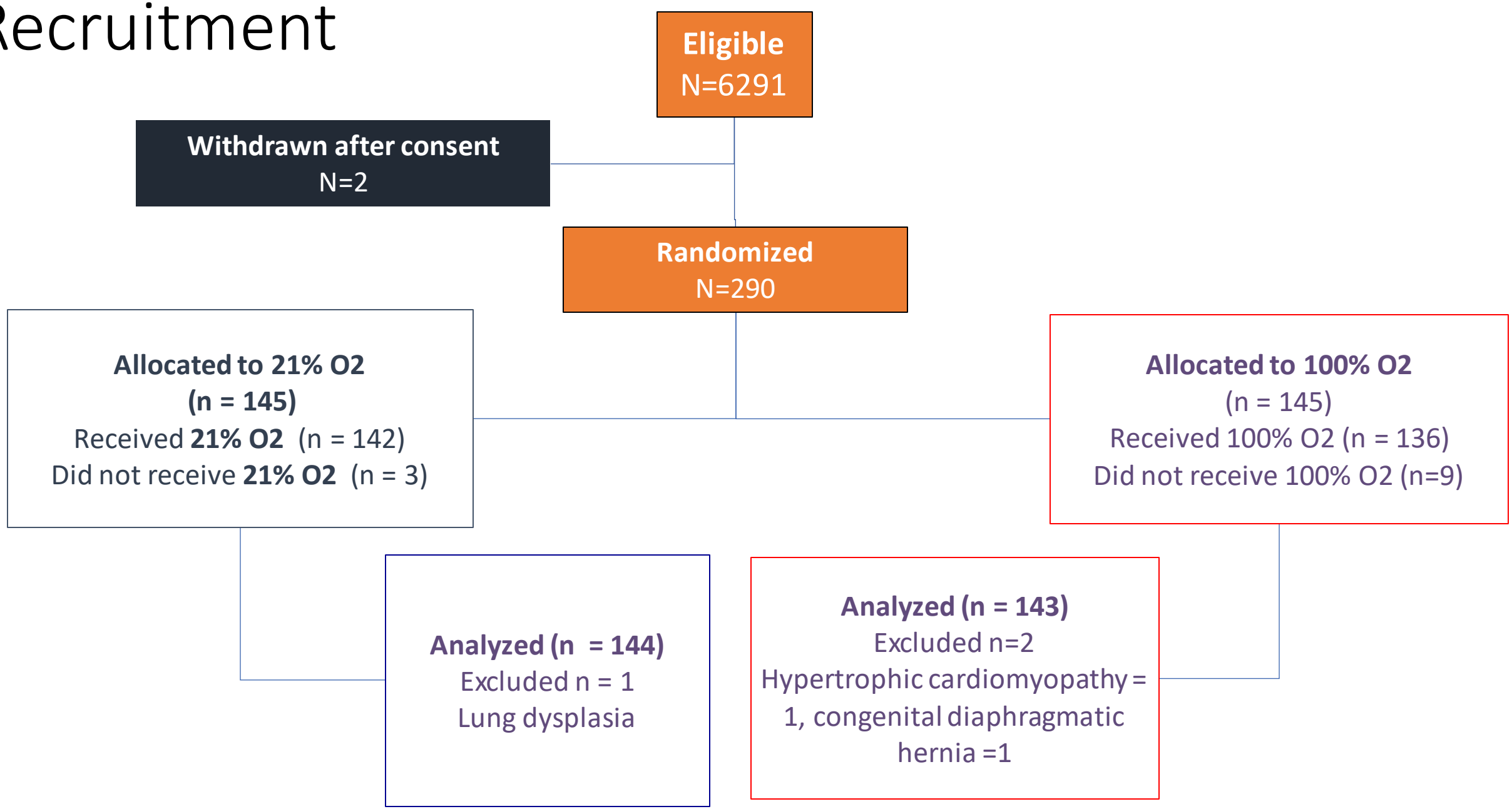

Resuscitation Guidelines Change
Funding
Resuscitation Guidelines Change
2005
2006
2007
2008
2009
2010
2015
Torpido study concept
Recruitment

DSMC Recommendations

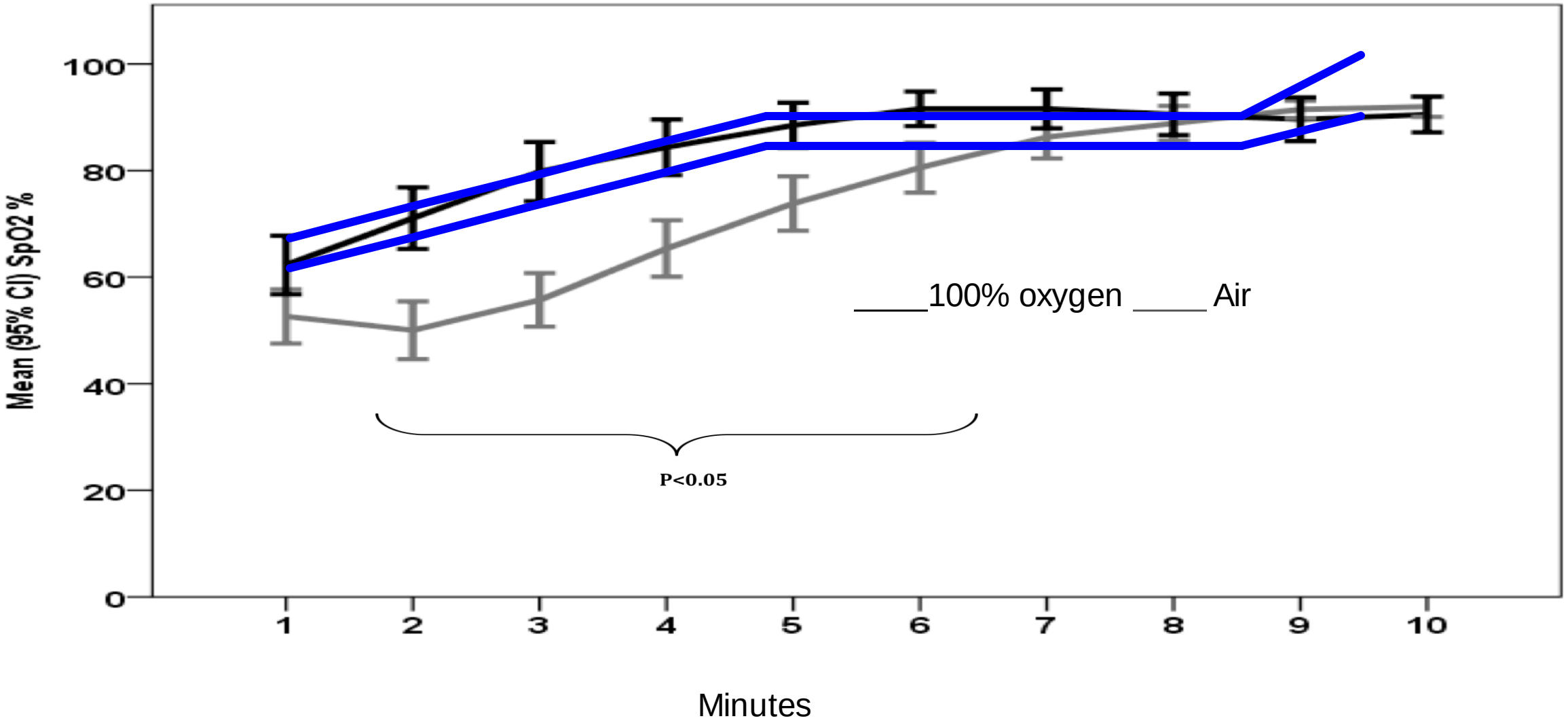
- Data and Safety Management Committee recommended in 2014 that recruitment be ceased at 292 patients due to slow recruitment as centers were reluctant to use 100% O_2 after publication of the 2010 ILCOR guidelines

- **As the Primary Outcome was not yet available,** short-term outcomes should be reported.

Recruitment

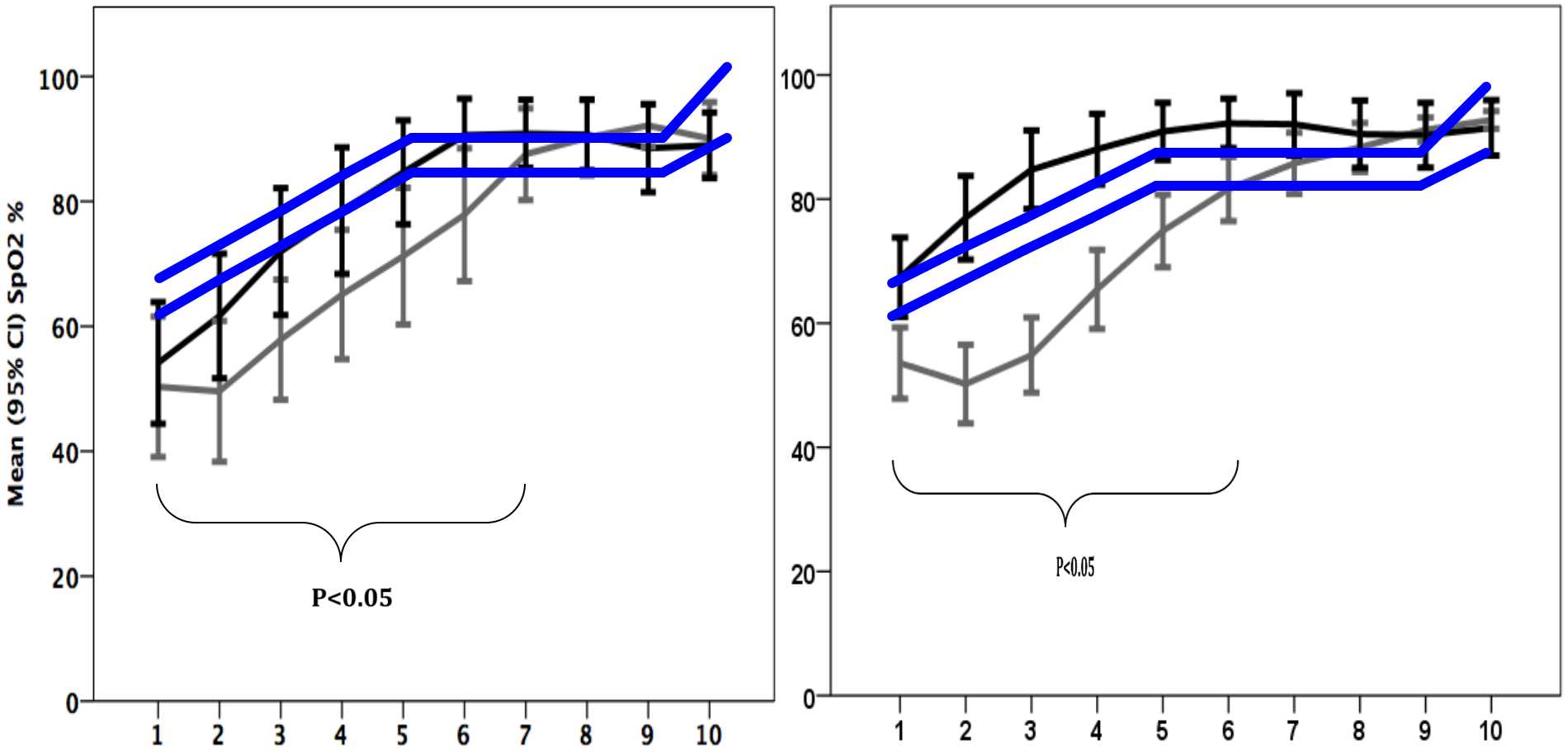


Oxygen Saturations – 1st 10 Minutes – All Babies



Oxygen Saturations - First 10 Minutes

____100% oxygen ____ Air



< 28 weeks gestation

≥ 28 weeks gestation

POST HOC- Hypothesis Generating Only
Hospital Mortality

- There was an **unexpected increase** in hospital mortality in infants <28 weeks gestation initially resuscitated with air.
- These are **not pre-specified and are marginally statistically significant**
- No infant >29 weeks died

	21% O2	**100% O2**	**Relative Risk (RR) [95% CI]**	**P**
<28 weeks	10/46 (22%)	3/54(6%)	3.9 (1.1-13.3)	0.03
>28 weeks	4/98 (4%)	2/89 (2%)	1.8 (0.3-9.6)	0.68

Is lower oxygen really better for preterm babies?

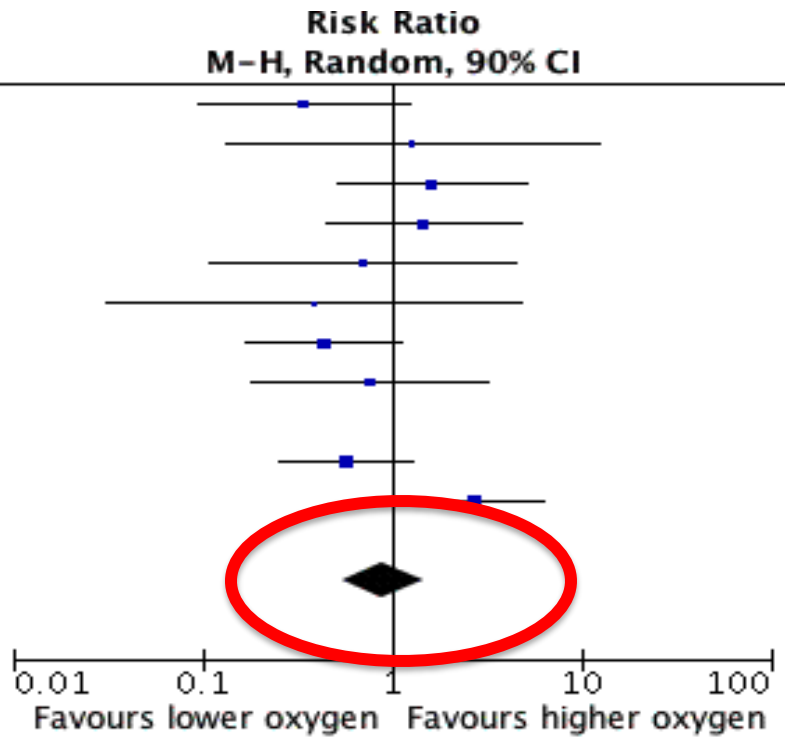
- **11 Studies**
- **$FiO_2 \leq 0.3$ v $FiO_2 \geq 0.6$**
- **NO STUDY OF FiO_2 between 0.3 to 0.4**

DEATH is not different in 970 infants <33 weeks gestation resuscitated with FiO_2<30% vs >60%

Study or Subgroup	Lower Oxygen Events	Lower Oxygen Total	Higher Oxygen Events	Higher Oxygen Total	Weight	Risk Ratio M-H, Random, 90% CI	Year
Lundstrom 1995	2	34	6	35	9.0%	0.34 [0.10, 1.24]	1995
Wang 2008	1	18	1	23	3.2%	1.28 [0.13, 12.34]	2008
Escrig 2008	4	19	3	23	10.9%	1.61 [0.51, 5.09]	2008
Vento 2009	4	37	3	41	10.2%	1.48 [0.45, 4.90]	2009
Rabi 2011	1	34	3	72	4.6%	0.71 [0.11, 4.57]	2011
Kumar 2012	0	5	1	6	2.6%	0.39 [0.03, 4.86]	2012
Aguar 2013	4	34	7	26	15.2%	0.44 [0.17, 1.12]	2013
Kapadia 2013	2	26	3	30	7.4%	0.77 [0.18, 3.23]	2013
Armanian 2013	0	14	0	13		Not estimable	2013
Rook 2014	6	99	10	94	18.8%	0.57 [0.25, 1.29]	2014
Oei 2015	14	144	5	143	18.1%	2.78 [1.21, 6.41]	2015
Total (95% CI)		**464**		**506**	**100.0%**	**0.90 [0.55, 1.48]**	
Total events	38		42				

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 10.54$, df = 9 (P = 0.31); $I^2 = 15\%$

Test for overall effect: Z = 0.41 (P = 0.68)



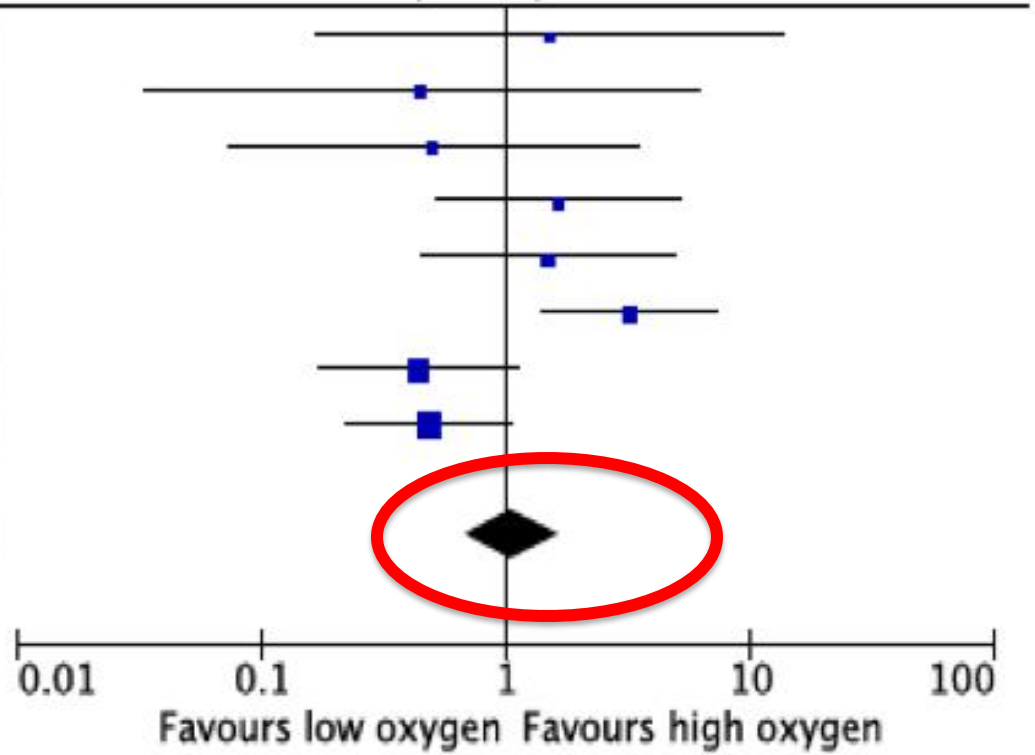
RR 0.90 (90% CI 0.55-1.45, p = NS)

Death in 509 infants <29 weeks gestation resuscitated with FiO_2<30% vs >60% was also not different

Study or Subgroup	Low oxygen Events	Total	High oxygen Events	Total	Weight	Risk Ratio M-H, Fixed, 90% CI
Wang	1	8	1	12	2.4%	1.50 [0.17, 13.56]
Rabi	0	11	1	15	3.8%	0.44 [0.03, 6.05]
Kapadia	1	15	2	15	6.0%	0.50 [0.07, 3.42]
Escrig	4	19	3	23	8.1%	1.61 [0.51, 5.09]
Vento	4	37	3	41	8.5%	1.48 [0.45, 4.90]
Oei	14	74	5	84	14.0%	3.18 [1.41, 7.19]
Aguar	4	34	7	26	23.7%	0.44 [0.17, 1.12]
Rook	6	53	10	42	33.4%	0.48 [0.22, 1.04]
Total (95% CI)		**251**		**258**	**100.0%**	**1.05 [0.68, 1.62]**
Total events	34		32			

Heterogeneity: $Chi^2 = 11.52$, $df = 7$ ($P = 0.12$); $I^2 = 39\%$

Test for overall effect: $Z = 0.21$ ($P = 0.83$)



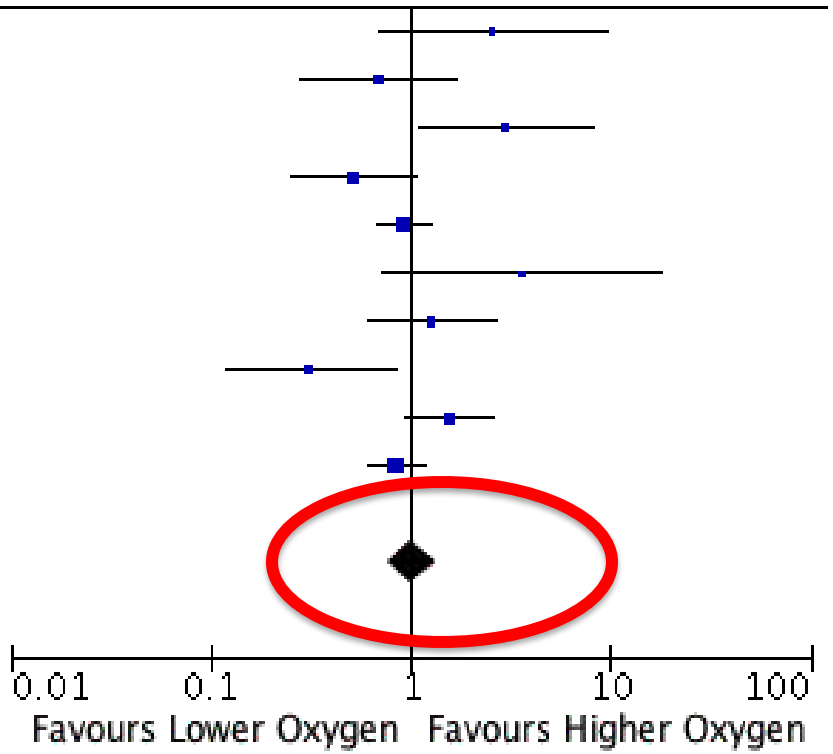
RR 1.05 (90% CI 0.68,1.62, p = NS)

BPD is not different in 939 infants <33 weeks gestation resuscitated with FiO_2<30% vs >60%

Study or Subgroup	Lower Oxygen Events	Lower Oxygen Total	Higher Oxygen Events	Higher Oxygen Total	Weight	Risk Ratio M-H, Random, 90% CI	Year
Lundstrom 1995	5	34	2	35	3.9%	2.57 [0.69, 9.61]	1995
Escrig 2008	4	19	7	23	7.2%	0.69 [0.28, 1.69]	2008
Wang 2008	7	18	3	23	6.0%	2.98 [1.09, 8.19]	2008
Vento 2009	6	37	13	41	9.7%	0.51 [0.25, 1.05]	2009
Rabi 2011	18	33	41	69	20.5%	0.92 [0.67, 1.25]	2011
Kumar 2012	3	5	1	6	2.7%	3.60 [0.71, 18.14]	2012
Aguar 2013	10	34	6	26	9.5%	1.27 [0.61, 2.65]	2013
Kapadia 2013	3	26	11	30	6.3%	0.31 [0.12, 0.84]	2013
Rook 2014	23	99	14	94	14.5%	1.56 [0.94, 2.58]	2014
Oei 2015	34	144	40	143	19.8%	0.84 [0.61, 1.18]	2015
Total (90% CI)		**449**		**490**	**100.0%**	**1.01 [0.76, 1.33]**	
Total events	113		138				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 16.06$, df = 9 (P = 0.07); $I^2 = 44\%$

Test for overall effect: Z = 0.05 (P = 0.96)



RR 1.01 (90% CI 0.76,1.33, p = NS)

It that it?
What about SpO_2?

SpO_2 Targets
Neonatal Resuscitation Program = Also no RCT

Time	SpO_2
1 minute	60-65%
2 minutes	65-70%
3 minutes	70-75%
4 minutes	75-80%
5 minutes	80-85%
10 minutes	85-95%

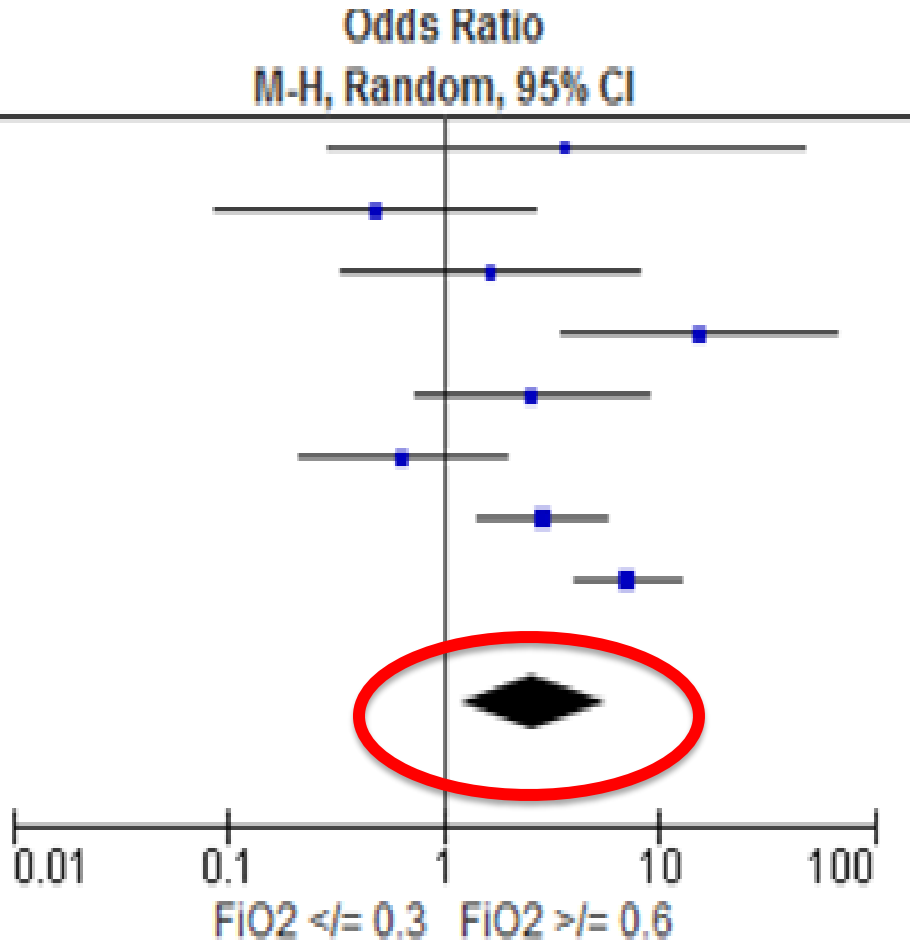
Only 23% of babies reached study targets

(But they were 2.6 times more likely to reach SpO_2 80% if started on higher oxygen)

Study or Subgroup	FiO2 </= 0.3 Events	Total	FiO2 >/= 0.6 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Wang 2008	2	10	1	16	6.3%	3.75 [0.29, 47.99]
Aguar 2013	29	34	24	26	10.0%	0.48 [0.09, 2.72]
Rabi 2011	5	11	5	15	10.7%	1.67 [0.34, 8.26]
Kapadia 2013	15	23	3	28	11.5%	15.63 [3.58, 68.18]
Escrig 2008	11	19	8	23	13.0%	2.58 [0.74, 9.01]
Vento 2009	28	37	34	41	14.0%	0.64 [0.21, 1.94]
Rook 2014	37	78	17	71	16.8%	2.87 [1.42, 5.79]
Oei 2015	82	140	22	134	17.7%	7.20 [4.08, 12.69]
Total (95% CI)		**352**		**354**	**100.0%**	**2.63 [1.21, 5.74]**
Total events	209		114			

Heterogeneity: $Tau^2 = 0.81$; $Chi^2 = 25.62$, df = 7 (P = 0.0006); $I^2 = 73\%$

Test for overall effect: Z = 2.44 (P = 0.01)

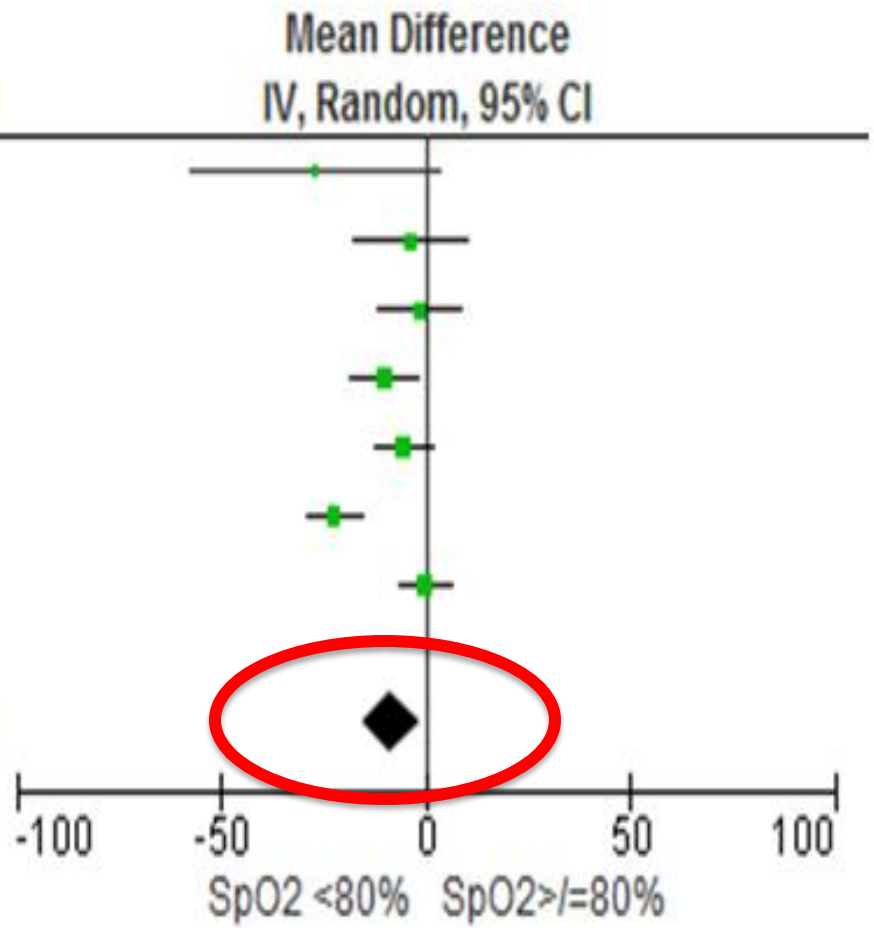


Babies with SpO_2 <80% at 5 min had lower (8 bpm) heart rates

Study or Subgroup	SpO2 <80% Mean	SD	Total	SpO2 >/=80% Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rabi 2011	131.5	47.5	10	158.4	14.7	16	4.6%	-26.90 [-57.21, 3.41]
Wang 2008	146	5.6	3	149.8	25.7	17	11.9%	-3.80 [-17.56, 9.96]
Vento 2009	146.8	16.7	62	148.2	18.3	16	15.0%	-1.40 [-11.28, 8.48]
Aguar 2013	168.2	16.6	53	178.3	9.3	7	16.3%	-10.10 [-18.31, -1.89]
Kapadia 2013	138.8	13.4	18	144.1	10.7	33	17.1%	-5.30 [-12.49, 1.89]
Oei 2015	122.8	32.1	103	145.1	19.5	169	17.4%	-22.30 [-29.16, -15.44]
Escrig 2008	165.4	9.6	19	165.6	12.1	23	17.6%	-0.20 [-6.76, 6.36]
Total (95% CI)			268			281	100.0%	-8.37 [-15.73, -1.01]

Heterogeneity: $Tau^2 = 68.88$; $Chi^2 = 26.43$, df = 6 (P = 0.0002); $I^2 = 77\%$

Test for overall effect: Z = 2.23 (P = 0.03)

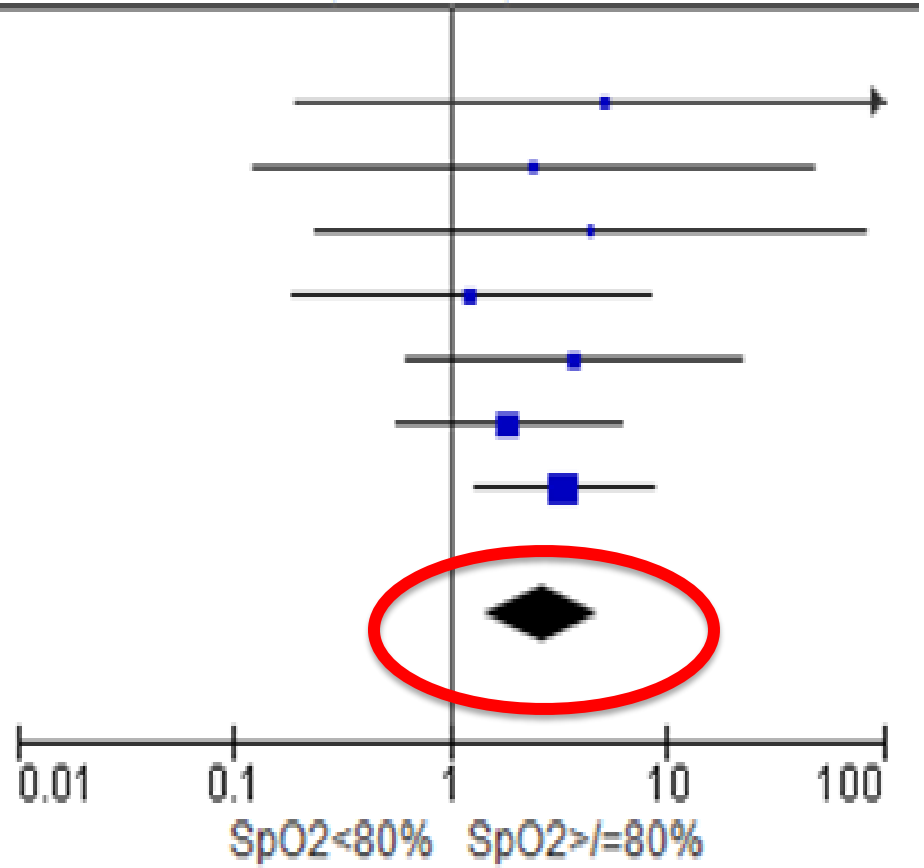


Babies with SpO_2 <80% at 5 min were more likely to die

Study or Subgroup	SpO2<80% Events	Total	SpO2>/=80% Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Wang 2008	0	3	0	23		Not estimable
Rabi 2011	1	10	0	16	3.4%	5.21 [0.19, 141.08]
Aguar 2013	7	53	0	7	4.2%	2.42 [0.12, 46.91]
Vento 2009	7	62	0	16	4.3%	4.46 [0.24, 82.27]
Kapadia 2013	2	18	3	33	10.3%	1.25 [0.19, 8.27]
Escrig 2008	5	19	2	23	11.6%	3.75 [0.64, 22.10]
Rook 2014	6	54	6	95	26.1%	1.85 [0.57, 6.06]
Oei 2015	13	104	7	170	40.2%	3.33 [1.28, 8.64]
Total (95% CI)		**323**		**383**	**100.0%**	**2.66 [1.45, 4.87]**
Total events	41		18			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.61$, $df = 6$ ($P = 0.95$); $I^2 = 0\%$

Test for overall effect: $Z = 3.17$ ($P = 0.002$)



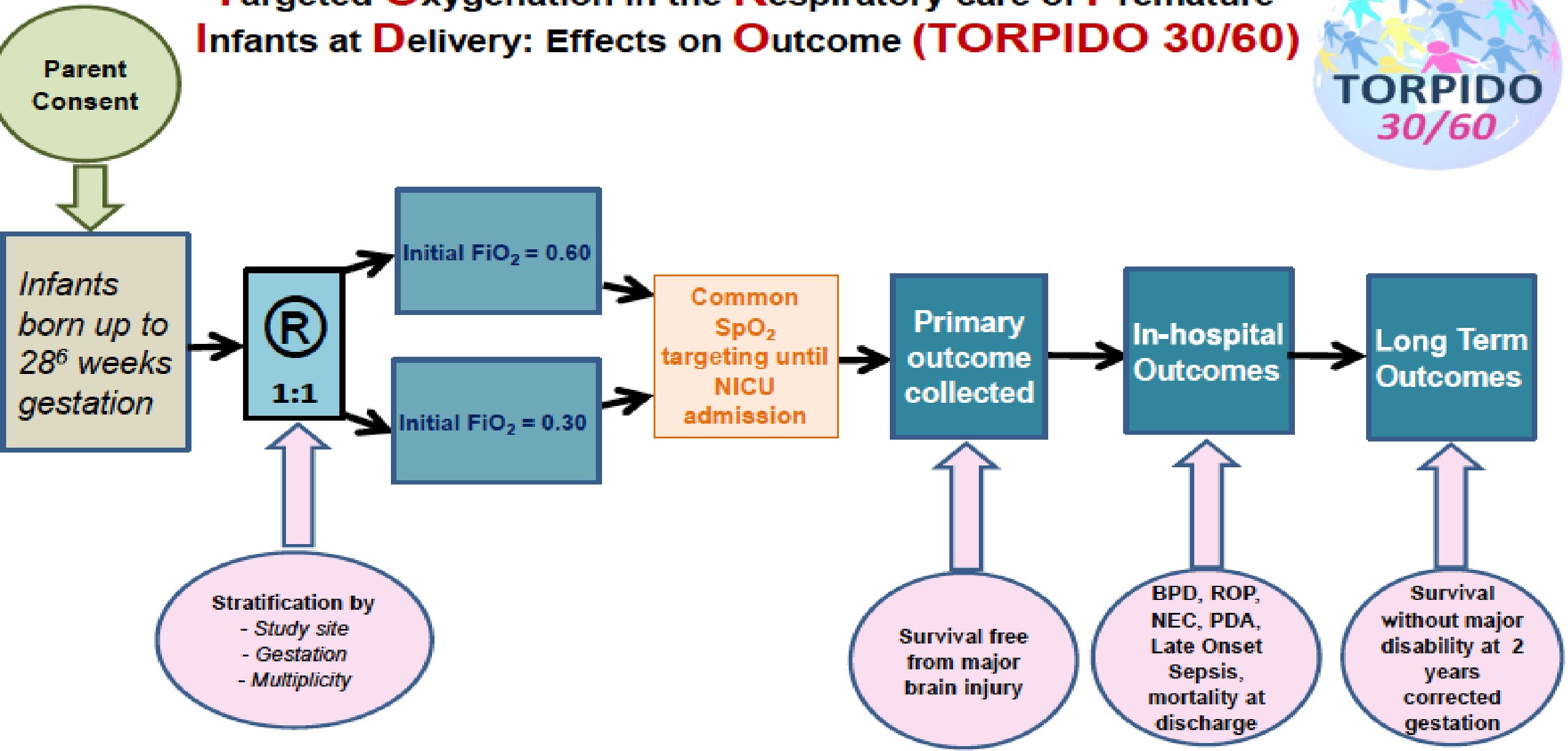
Many Questions Remain

Is it starting FiO_2?

What about SpO_2?

We need to do an RCT!

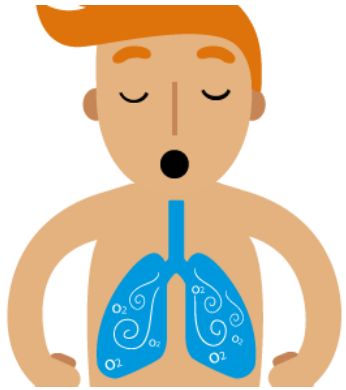
Targeted Oxygenation in the Respiratory care of Premature Infants at Delivery: Effects on Outcome (TORPIDO 30/60)

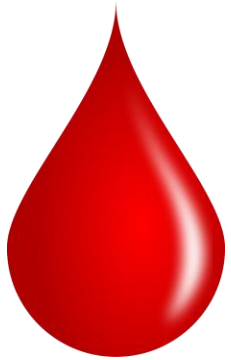


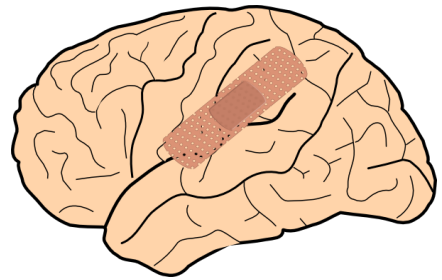
For further details contact **Rebecca Brown:** Torpido3060@ctc.usyd.edu.au

Hypoxic Ischemic Encephalopathy (HIE)

Hypoxic + Ischemic = Encephalopathy







Not Enough Oxygen

Not Enough Blood

Brain Injury

Severe HIE Accounts for ¼ of All Global Neonatal Deaths (>900,000 p.a.)

~50% with severe HIE will die

~ 20% will have major disability

>70% of survivors without major disability will have cognitive and other problems e.g. Autism and behavioral issues that significantly impair daily function

Therapeutic Hypothermia (TH)

Cool body or head to 33-34°C

Maintain 72 hours

Metabolic rate slows

Brain cells recover

Therapeutic Hypothermia

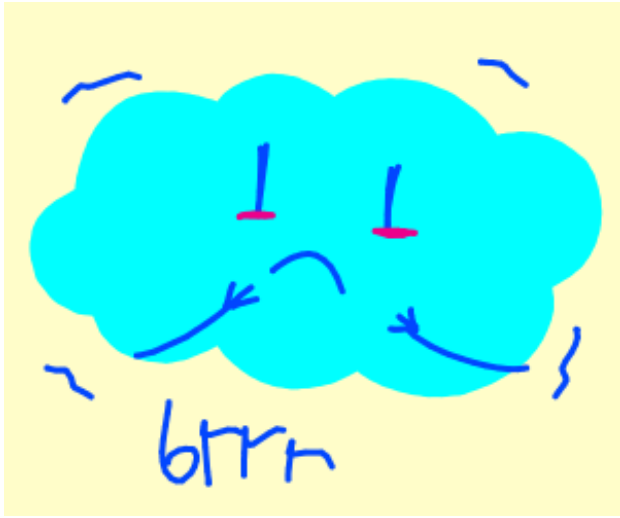
Each ↓2-4° *systemic or selective brain temperature = improved survival after adult stroke, trauma, cardiac arrest*

↓

- **Cerebral energy metabolism**
- **Free radical production**
- **Glutamate release** (glutamate causes seizures)

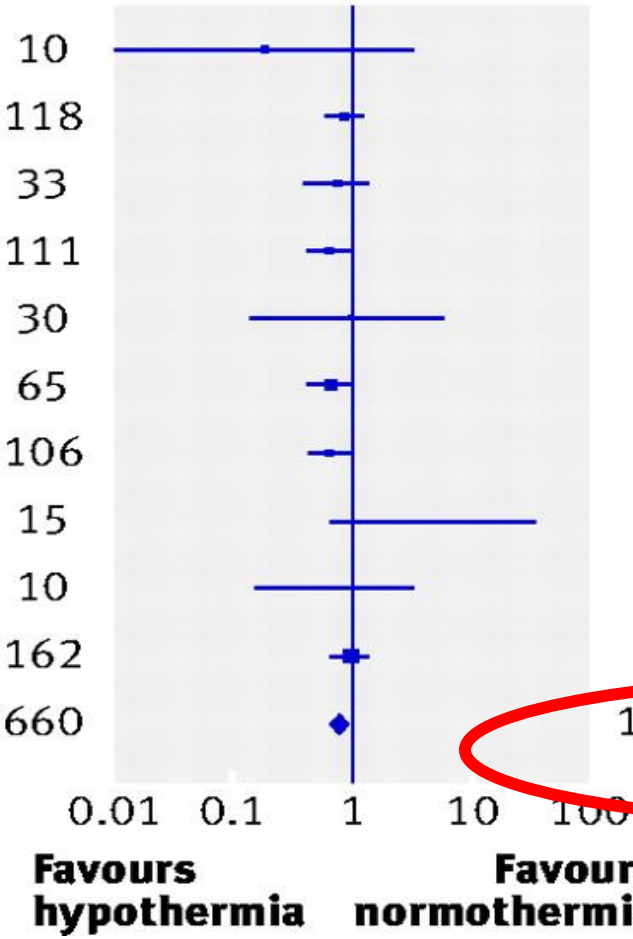
↑

- N-acetyl aspartate (controls brain fluid, source of lipid for myelin synthesis, low levels associated with brain injury)
- **Protein synthesis**
- **Preserves**
  - Antioxidants
  - Cerebral ATP

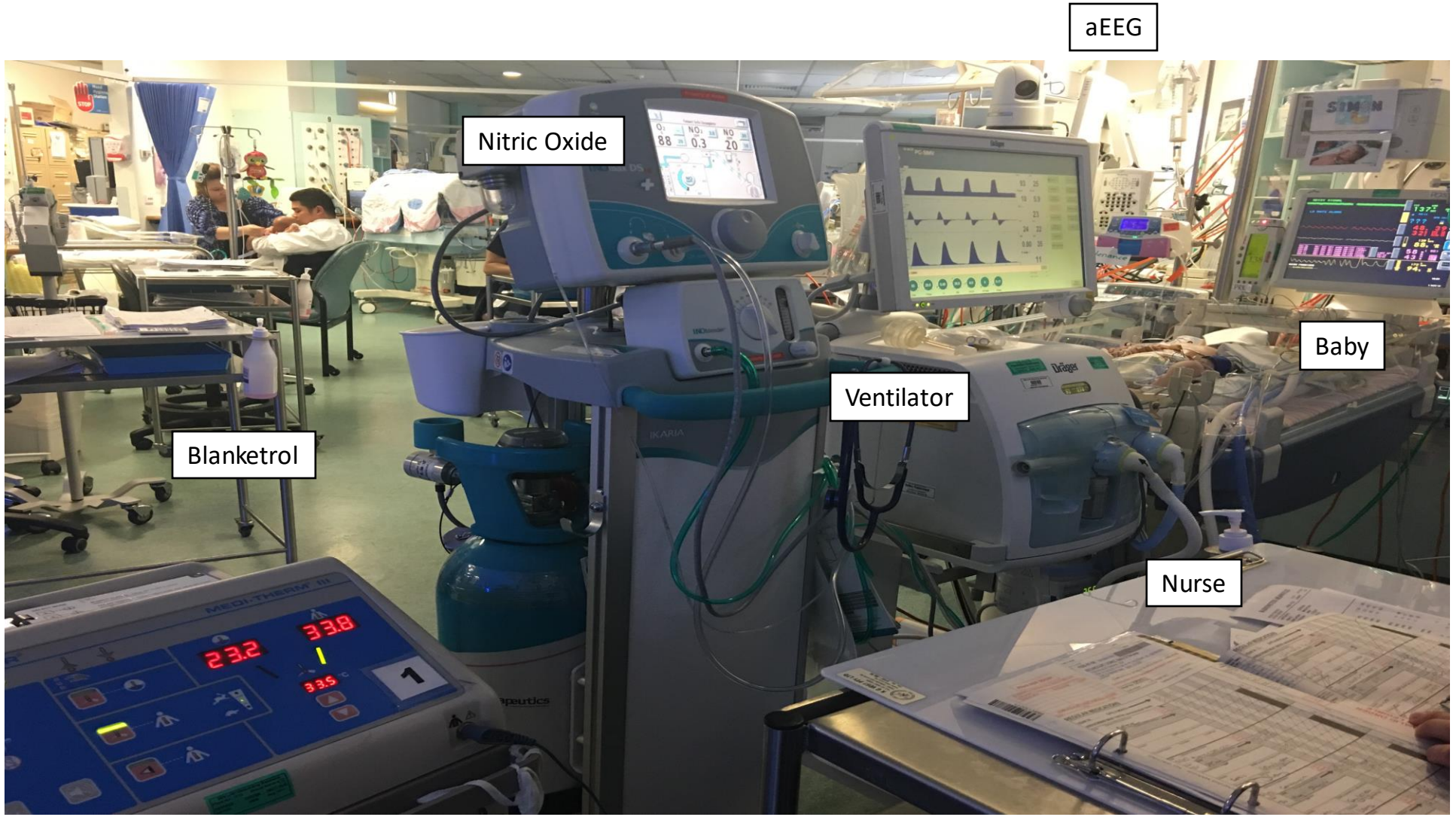


TH Decreases Death after SEVERE HIE

Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Akisu	0	11	2	10		1.2	0.18 (0.01 to 3.41)
CoolCap	36	116	42	118		19.3	0.87 (0.61 to 1.25)
Eicher	10	32	14	33		6.4	0.74 (0.38 to 1.41)
ICE	25	110	39	111		18.0	0.65 (0.42 to 0.99)
Lin	2	32	2	30		1.0	0.94 (0.14 to 6.24)
neo.nEURO	21	64	32	65		14.7	0.67 (0.43 to 1.02)
NICHD	24	102	38	106		17.2	0.66 (0.43 to 1.01)
Robertson	7	21	1	15		0.5	5.00 (0.69 to 36.50)
Shankaran	2	9	3	10		1.3	0.74 (0.16 to 3.48)
TOBY	42	163	44	162		20.4	0.95 (0.66 to 1.36)
Total (95% CI)		660		660		100.00	0.78 (0.66 to 0.93)
Total events	169		217				



TH is Hard Work



Therapeutic Hypothermia has Side Effects

- Meta-analyses of 1322 infants, 11 studies
- Cardiac arrhythmia (RR 2.42, 95% CI: 1.23-4.76), especially Sinus Bradycardia, Ventricular arrhythmias, hypotension
- Thrombocytopenia (RR 1.18, 95% CI: 1.02-1.37) and coagulopathy
- Metabolic dysfunction: acidosis, hypokalemia, hypoglycaemia
- Seizures

Therapeutic Hypothermia must start within 6 hours

MALE INFANT

- 39 Weeks
- Spontaneous labour
- Poor fetal trace
- Cesarean Delivery
- IPPV at birth
- APGAR 3 (1), 5 (5), 8 (10)
- Cord Ph 6.9 Lactate 17
- Admitted to nursery for observation
- Very alert
- Not cooled
- Sent to the Postnatal Ward by 7 hours

Seizures 12 hours

MRI
Occipital Changes
day 5

The Mild Child

Is ”Mild” Really “Mild”?

Studies	n	Mild	Cooled	Abnormal
All	20	314	46	25%
Cohort	16	250	0	**22%**
Trials	2	91	46	29% v 37% (NS)

Conway 2018

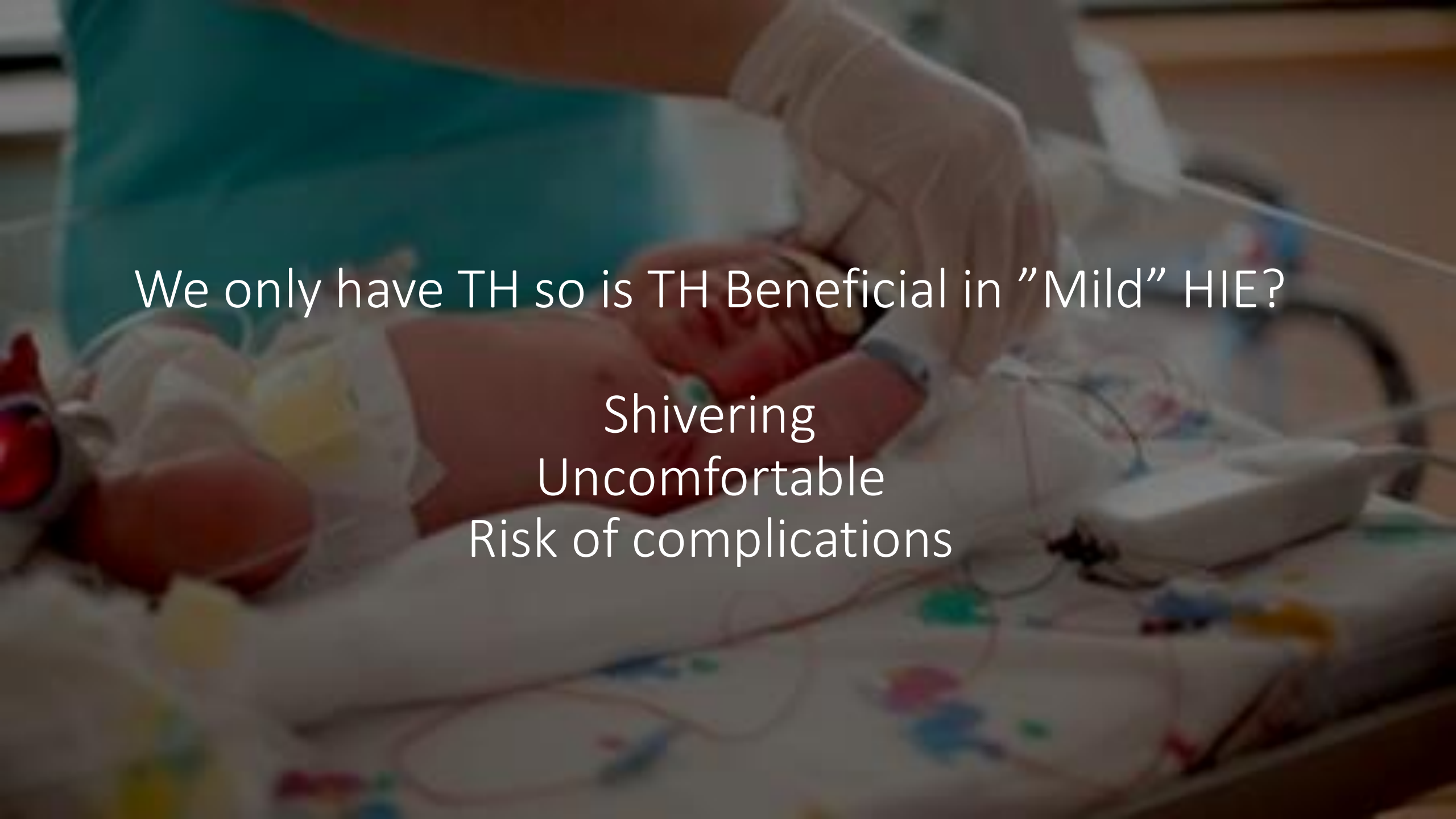
Prospective Research in Infants with Mild Encephalopathy (PRIME) study

- Only cohort study with follow-up
- 54 infants
- > 1 abnormality on modified Sarnat score
- Aeeg = Normal in 50
- 1 = mod HIE (initial normal aEEG)
- 43/53 (68%) followed up = 16% disabled
- 56% at least one BSID <1 SD below mean
- Disability associated with abnormal MRI and discharge examination

Lina Chalak
Texas

Neurodevelopment in ”Mild” HIE

- Abnormal neurodevelopment seen in 10-30% with mild HIE
- 50% mild HIE at school age have MRI abnormalities at 9-10 y
  - Thalamic NAA/Cr ratio (marker of neuronal death)
  - NAA/Cho ratio (Loss of cell membrane integrity)
  - White matter injury
- Lower IQ
- Increased thought/behavior problems



We only have TH so is TH Beneficial in ”Mild” HIE?

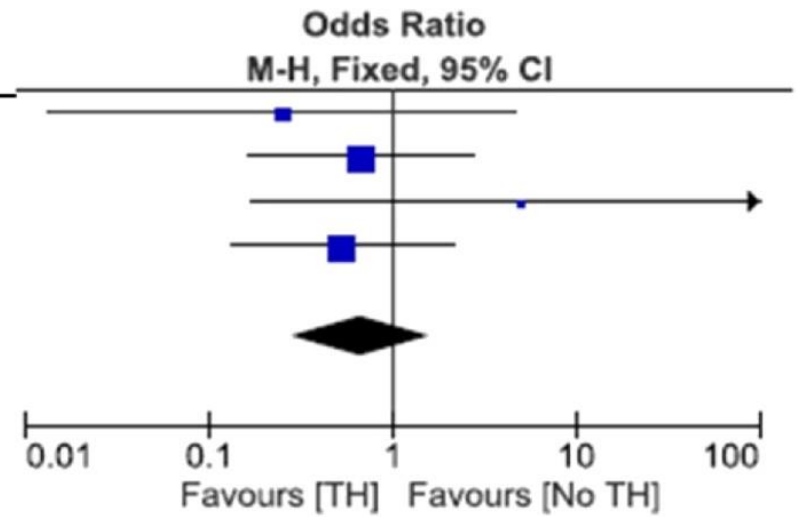
Shivering
Uncomfortable
Risk of complications

Cooling for Mild HIE
No current evidence for benefit from studies of severe HIE

	Therapeutic Hypothermia		Control			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Battin,M 2001	1	5	2	4	14.5%	0.25 (0.01, 4.73)
Jacobs,S 2011	4	16	8	24	39.1%	0.67 (0.16, 2.74)
Wyatt,J 2007	2	5	0	3	2.8%	5.00 (0.17, 146.64)
Zhou,W 2010	6	19	7	15	43.6%	0.53 (0.13, 2.14)
Total (95% CI)		45		46	100%	0.67 (0.28, 1.61)
Total Events	13		17			

Heterogeneity Chi^2 =1.90, df = 3 (P = 0.59), I^2 = 0%

Test for overall effect Z = 0.90 (p = 0.37)



But Therapeutic Creep Is Here

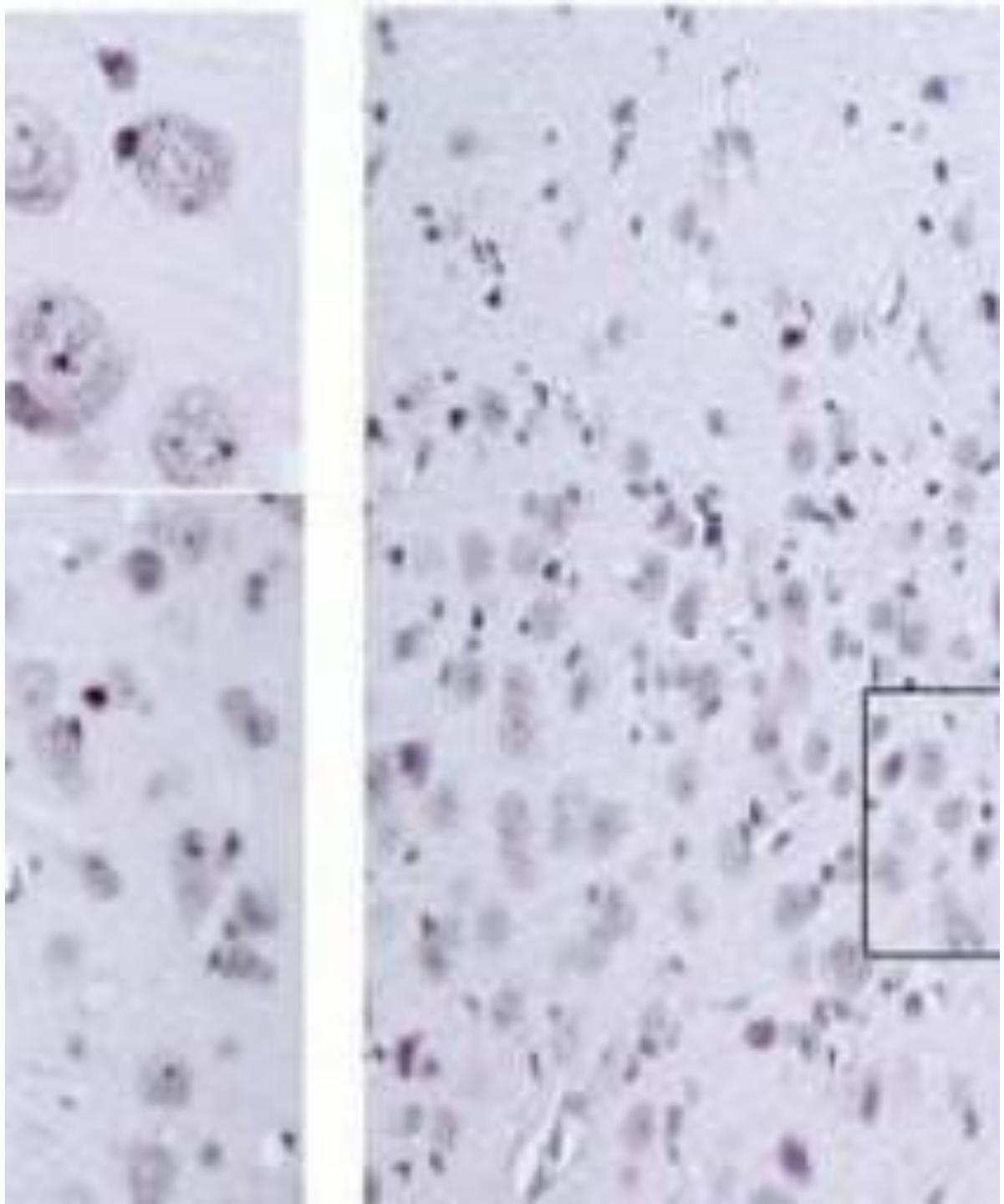
UK SURVEY (Oliveira 2018)

- 48/74 NICUs surveyed
- 36 (75%) offered cooling to ”mild” HIE and out of criteria babies (>12 hours)
- 13 (36%) discontinued TH <72 hours
- 29 (80%): MRI
- 27 (75%): neurodevelopmental follow-up

TH can be harmful

Cooling piglets without hypoxic injury:

- Neuronal injury
- Neuronal loss in anterior putamen + motor cortex



We Need an RCT

1. Definition
2. Broaden acidosis criteria: ph 7.1 and BD 10
3. aEEG
4. Biochemical markers e.g. serial lactates
5. Duration of cooling?
6. Sample size: Must be large enough to show relevant outcomes including neurodevelopmental injury

COMET: Cooling in Mild Encephalopathy Trial

- UK
- Aims to assess DURATION of TH in mild HIE
- A: 60 infants to normal care+ 60 to TH
- B: 80 infants without progression at 24-48 h to STOPPING TH or continuing
- Primary outcome: **MRS** at 1-2 weeks

TIME

- Therapeutic Hypothermia for Infants with Mild Encephalopathy
- 68 infants to TH or normal care
- Infants who progress to mod HIE will be crossed over to TH
- Primary outcome: neurodevelopment at 1 year

COMFI
Cooling for Mild HIE and the Future Neurodevelopment of Infants

- Multisite international study (unfunded currently)
- 52 hospitals from 10 Countries
- RCT of cooling v no cooling 72 h and up to 12 h of age
- 520 infants
- PRIMARY OUTCOME: 2 year neurodevelopment

But clinical trials in newborn babies are SO difficult

- Babies are totally dependent – need to wait for parents to consent
- Ethically fraught
- Time pressured – many studies, including resuscitation trials need to be done NOW
- High risk death and disability
- Small numbers - trials economically unattractive

Children are not little adults

- Different physiological, developmental, psychological and pharmacological characteristics
- Metabolism is different
  - Tetracyline = enamel dysplasia
  - Chloramphenical = Gray baby syndrome
  - Propylene glycol = metabolic acidosis
- They cannot give consent

There are not enough studies about infants

- **27%** world's population are children, pediatric trials = 16.7%
- Clinicaltrials.gov: 388,717 studies in 219 countries
- 6,073 (**1.5%)** studies with "newborn" +/- "neonate"
- 89% children live in LMIC **= 25%** pediatric trials in LMIC
- Children were classed as "**therapeutic or pharmaceutical orphans**" in the 1960's
- **65%** of drugs used in newborn infants are off label or unlicensed

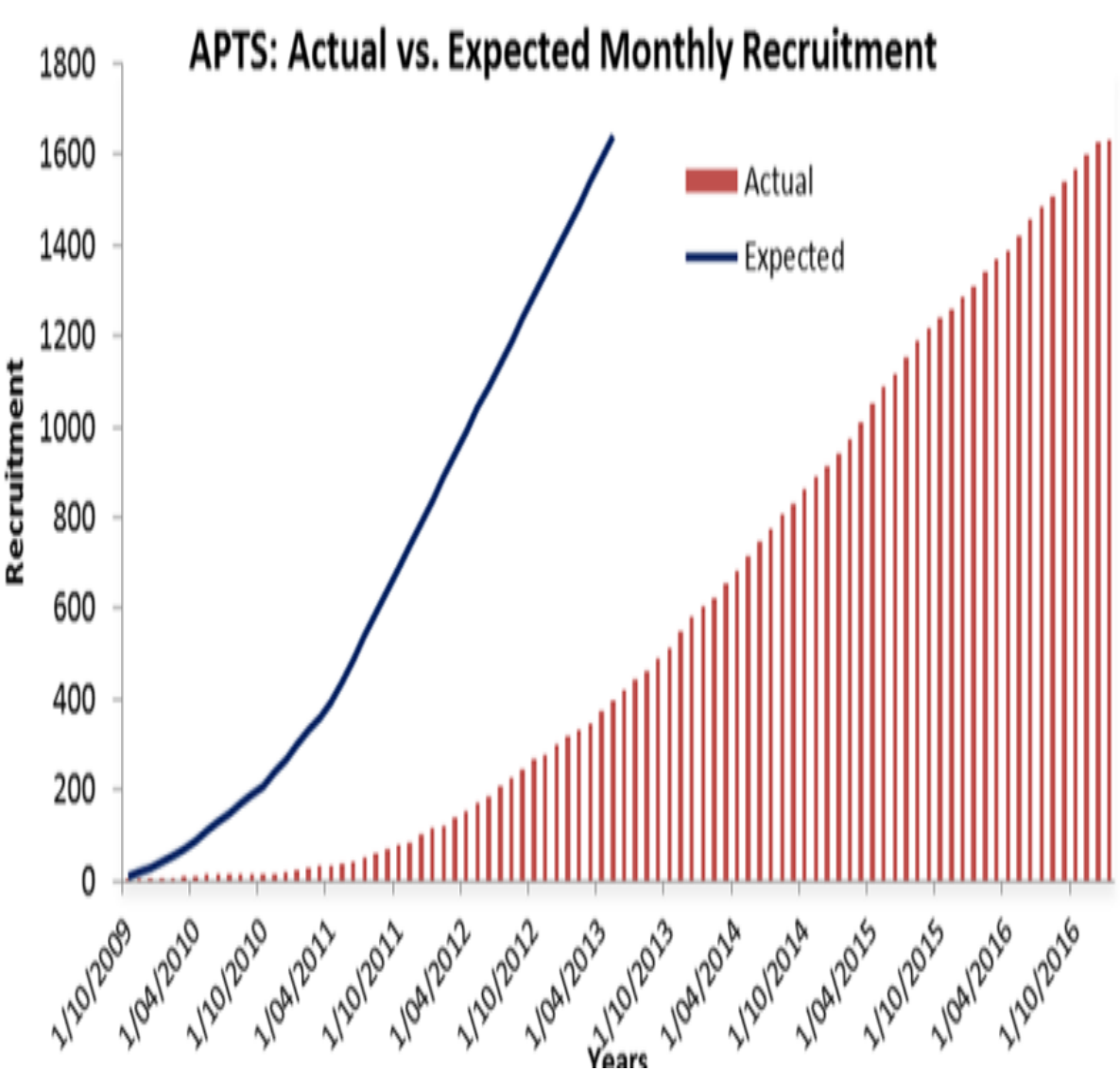
Trial design in babies need special considerations

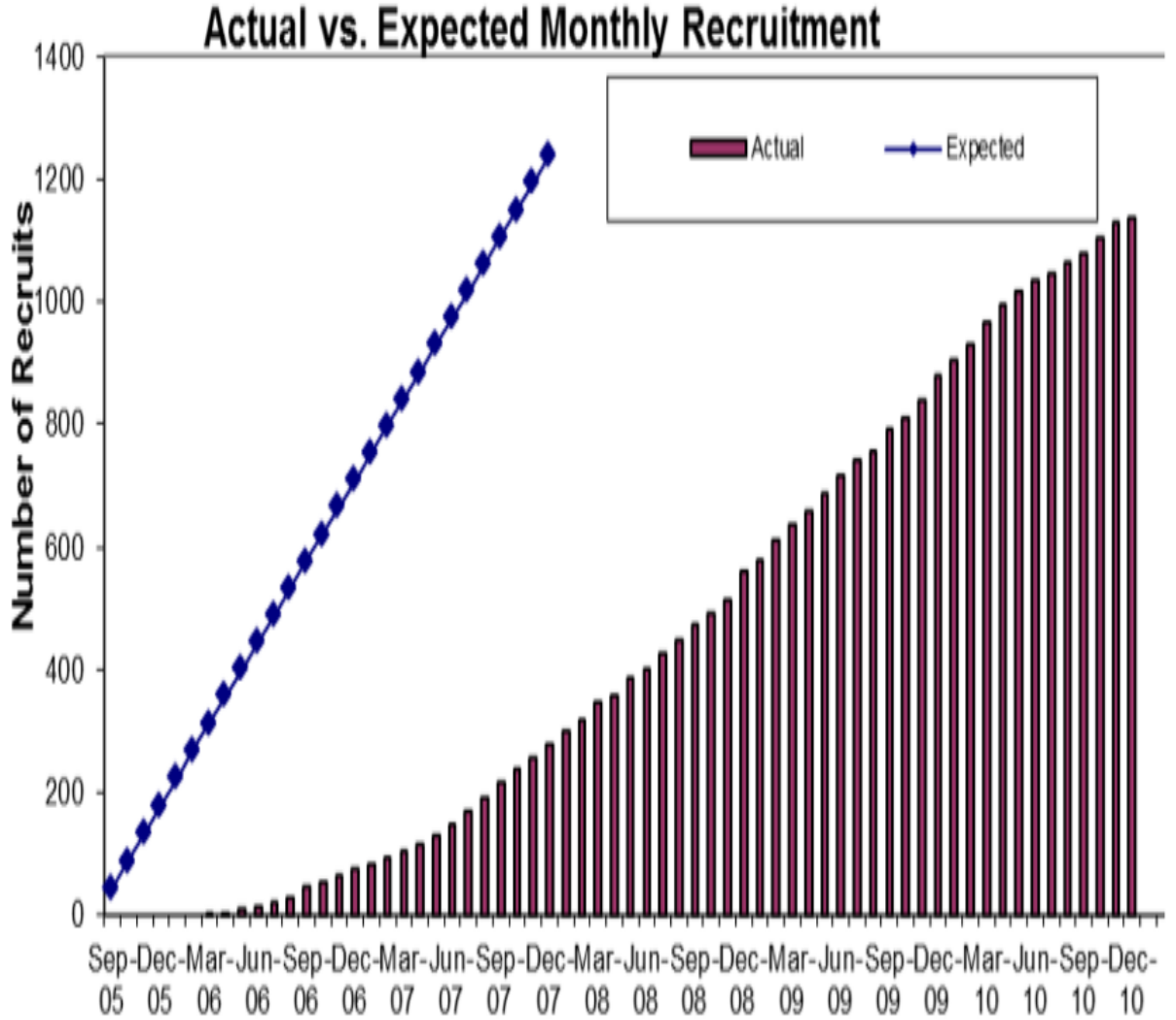
- Phase I studies (testing safety and pharmacokinetics) discouraged due to unknown effects
- May be acceptable only if condition is LIFE THREATENING or STANDARD THERAPIES have failed
- Testing in children often deferred to Phase 3 (evaluation of efficacy, acceptability, adverse effects aka RCT) to protect children from harm
- This also delays access to potentially useful medications
- Phase IV (post marketing trials) extremely rare
- Trial registration is poorly reported, many not published

Sample sizes are SMALL

- 38% of 746 pediatric trials from 1996 to 2002 = sample size >100
- Lower burden of disease
- Inconclusive results
- Fail to demonstrate important outcomes including adverse effects
- **Australian Placental Transfusion Study (APTS)** took 30 years and 17 RCTs since 1988 to show that DCC reduced death by 32% ($P<0.006$) in 2,834 preterm infants
- THOUSANDS of babies may be alive if this had gone faster

Figure 1: Actual vs Expected Recruitment in the NHMRC APTS and BOOST II trials





Parental MOTIVATION
The crucial step to a successful trial

- **Parents motivation to take part:**

1. Altruistic – doing good
2. Hope that own baby may benefit
3. Bring hope to a hopeless situation

- **Parents motivation for NOT taking part:**

1. Inconvenience
2. Burden for the child
3. Risks
4. Not enough time to decide
5. Infant's severity would not influence trial participation
6. Want input from others (e.g. spouse, wide family)

Parental EMOTIONS

- Stressful time
- Fear
- Confusion
- Vulnerability
- Pride in taking part
- Guilt for subjecting infant to a study
- Guilt for not subjecting infant to study
- Perception of burden varies
- Pressure to participate

The CLINICIAN Views of Parents

- Respect parental authority and rights
- Parents have to live with the long-term outcomes of their decisions
- Some felt that clinicians were best decision makers
- Some would prioritise infant interest over parental autonomy
- Some tried to spare parents the burden of making decision

Clinician views of TRIALS

- Consent process difficult
  - Time
  - Parental pressure
- Takes away time from urgent clinical duties
- Balancing responsibility to research v responsibility to parents and infant difficult
- Some thought trials raised false hopes
- Some think that someone else can do it

The CONSENT PROCESS is Different in Neonatal Trials: the Barriers

- Antenatal
  - More time to think
  - It will never happen to me
- In labour
  - Usually not acceptable
- Waived consent
  - Most not comfortable with this unless no other option
- Opt out
  - Half/half – more recruited via opt out
- Continuous
  - Initial agreement to participate but continuing discussion and further information after recruitment
  - May improve validity

Multiple Studies How many is too many?

- Will validity of individual trials be affected?
- Participation in multiple trials may lead to:

1. Detection errors (fail to describe and event because it is too rate)
2. Misattribution (falsely attribute an event to the trial)
3. Uncertainty (information not precise enough)

- Not additional stress on the infant (surprisingly)

When Should Multiple Trials be Avoided?

1. Each trial looking at a novel therapy that is not well described (e.g. not approved or not marketed)
2. Trials have similar primary end points
3. Each trial targets the same organ

When Should Multiple Trials be Considered?

1. Brief pharmacokinetic and/or safety studies
2. Device validation studies
3. Factorial studies with adequate sample sizes
4. Trials of routinely used and standard interventions

Parental Views of Multiple Studies

- No data to say that parents are stressed or consider it unethical to be approached for multiple studies
- >75% consider it acceptable to take part in >1 study

Research Culture in the Unit

- Some units have a research culture despite busy clinical loads
- **Research Champions** are excellent in promoting research, studies and trouble shoot obstacles raised by the clinical team
- Clinical team is usually too busy to do much research
- Avoid throwaway comments like “guinea pigs”
- Brief staff about each project e.g. trial not opened until >80% of staff are briefed. This may take weeks

Clinical Networks Connecting Us Together

- **Research networks provide one stop shops to overcome issues in clinical trials**
- European Network for Paediatric Research at the Euroepan Medicines Agency (EnprEMA)
- Global Research in Paediatrics (GRuP) Network of Excellence (European)
- US Pediatric Trials Network
- US Consortium Child Health Oversight Committee of the Clinical and Translational Science Awards
- **Japan Neonatal Research Network**

Outcomes of Interest

Table 1: The top nine outcomes from GONet and COIN.

Preterm Birth Core Outcomes	Core Outcomes in Neonatology (COIN)
Offspring mortality	**Survival**
Offspring infection	Offspring infection
Gestational age at birth	Necrotising enterocolitis
Harm to offspring from intervention	Brain injury on imaging
Birth weight	Retinopathy of Prematurity
Early neurodevelopmental morbidity	**General gross motor ability**
Late neurodevelopmental morbidity	**General cognitive ability**
Gastro-intestinal morbidity	Visual impairment,
Respiratory morbidity	Pain

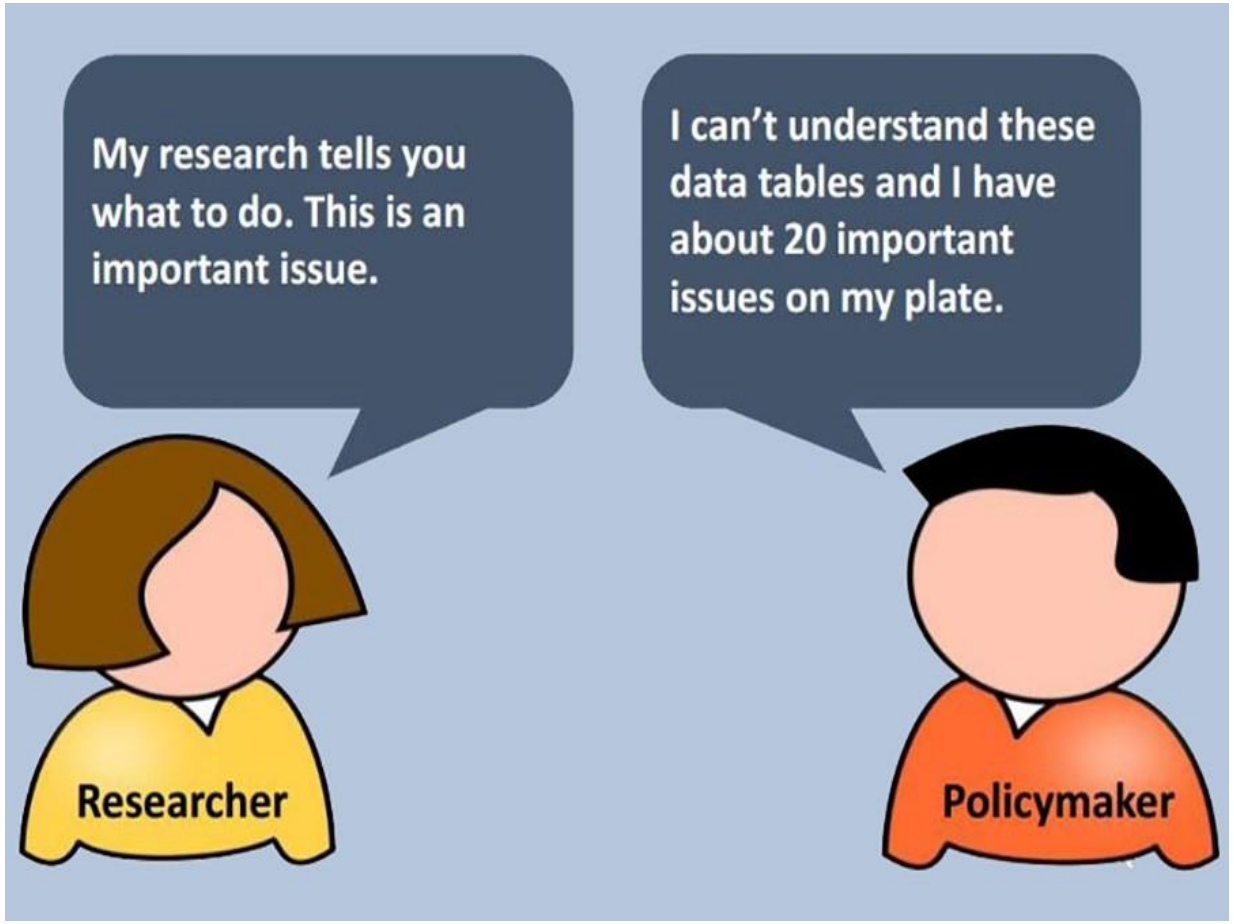
Collaboration is VITAL

- **>20,000 infants** are needed to show a clinically significant reduction of 20% in death from 5% to 4%

Event Rate in Control group (C)	Event Rate in Treatment Group (T)	Risk Difference (C-T =Δ)	Relative Risk or Risk Ratio (RR=T/C)	Relative Risk Reduction (1-RR)	Number needed to benefit or harm (100/ Δ)	TOTAL SAMPLE SIZE REQUIRED FOR 90% POWER			
						0% cross-over in each group	5% cross-over in each group	10% cross-over in each group	15% cross-over in each group
20%	16%	4%	0.8	0.2	25	3,868	4,776	6,044	7,894
20%	18%	2%	0.9	0.1	50	16,166	19,960	25,260	32,992
10%	8%	2%	0.8	0.2	50	8,598	10,616	13,436	17,548
10%	9%	1%	0.9	0.1	100	36,136	44,164	56,464	73,748
8%	6.4%	1.6%	0.8	0.2	63	10,964	13,536	17,132	22,376
8%	7.2%	0.8%	0.9	0.1	125	46,122	56,942	72,066	94,128
5%	4%	1%	0.8	0.2	100	18,058	22,294	28,216	36,854
5%	4.5%	0.5%	0.9	0.1	200	76,076	93,922	118,870	155,258

Results must be translated into policy and practice

- **Remove ineffective/harmful** interventions from practice
- Ensure equity of access to **effective and cost effective** interventions
- Facilitated by audit, benchmarking, QI activities embedded in regional, national or international networks
- Facilitate monitoring, peer referencing, risk adjusted outcomes
- **Highlight excellence**



Conclusions

- Clinical trials have been, and continue to be vital to improve the health of sick newborn infants
- **<u>Collaboration</u>** is necessary
- There are many questions in newborn medicine that if unanswered will lead to death and disability in THOUSANDS of the SICKEST INFANTS

Thank you

Trends in outcomes among very low birthweight infants in Japan from NRNJ database 2003-2016

Masanori Fujimura	Department of Neonatology, Osaka Women's & Children's Hospital
Satoshi Kusuda	Department of Pediatrics, Kyorin Medical University
Yumi Kono	Department of Pediatrics, Jichi Medical University
Hidehiko Nakanishi	Department of t Neonatology, Kitasato University Medical School
Shinya Hirano	Department of Neonatology, Osaka Women's & Children's Hospital
Naohiro Yonemoto	Department of Public Health, Juntendo University

This presentation tries in accordance with "the Reporting Outcomes of Extremely Preterm Births" (Matthew A. Rysavy, Neil Marlow, Lex W. Doyle et al, PEDIATRICS Volume 138, number 3, 2016: e2 0160689

Neonatal Research Network of Japan

NRNJ is a non-profit organization with main support from neonatal professions

2021

Disclosures

Dr. Masanori Fujimura has disclosed the following relationships.
Any real or apparent conflicts of interest related to the content of this presentation do not exist.

Organization
Consultation with Novelpharma (intravenous indomethacin) 1998~2003

Title	Trends in outcomes among very low birthweight infants in Japan from NRNJ database 2003-2016
Purpose	To analyze the NRNJ database for trends in outcomes of extreme-preterm infants, with a focus on 22 week.
Subjects	◆Very low birthweight infants ≦1,500g in Japan - Include infants born alive but died in the delivery room. ◆ N=60,632 (2003~2016), 65% of census of Japan. 99.9% were Japanese.
Definition	Database Operation Manual The developmental quotient (DQ) at 3 years was by chronological age.
Statistics	EZR. Significance of difference: *P<0.001*
Figures	Excel

Contents

1. Background, Study population
2. Trend of mortality and neurodevelopmental impairments
3. 22 week of gestation
4. Maternal factors
5. Neonatal factors

Background

Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks.

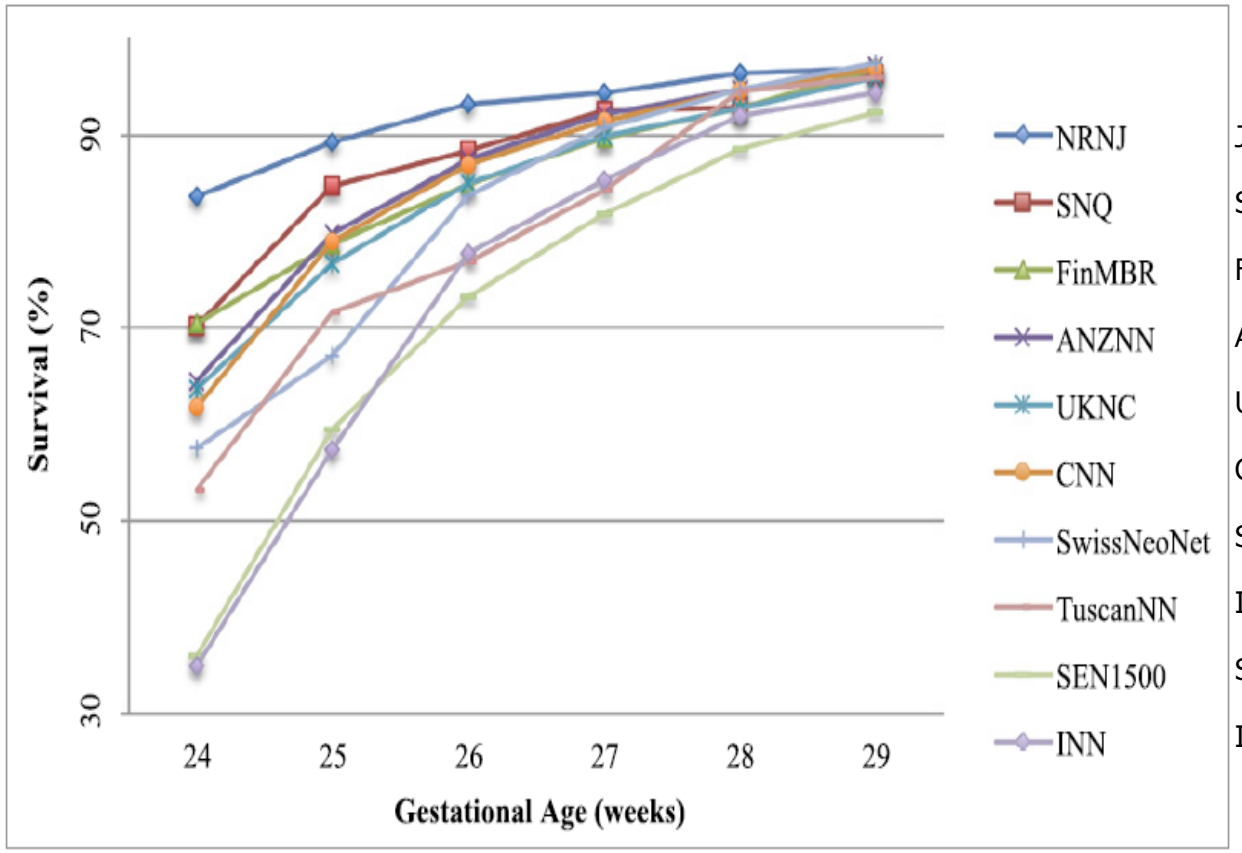


FIGURE 1

GA-specific survival for infants (24–29 weeks' gestation, birth weight <1500 g) born between 2007 and 2013 and admitted to neonatal care in the iNeo networks.

Helenius K, Sjörs G, Kusuda S et al. Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks. Pediatrics. 2017 Dec;140(6):e20171264. doi: 10.1542/peds.2017-1264.

The value of NRNJ database

Neonatal Research Network of Japan

Analysis of NRNJ database is one of the way to evaluate the real data of preterm infants for the evidence discovery.

Real-World Evidence | FDA https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions.

What is RWE?

Real-world ***evidence*** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

The value of NRNJ database is based on the facts;

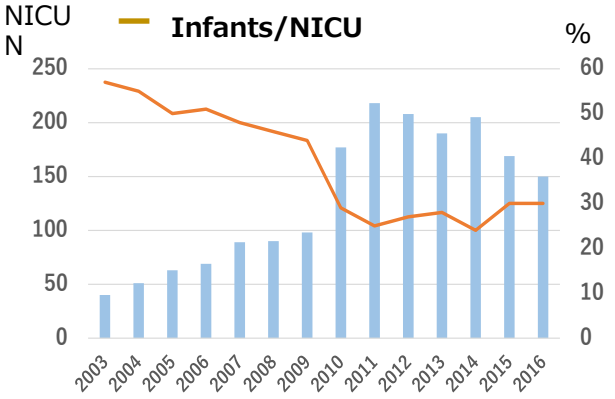
1. The observational study is now recognized to be a field to generate evidence.
2. Extreme prematurity is one of the major interests in neonatal medicine.
3. Neonatal care in Japan experience the frontier in preterm care. The NRNJ database currently contains appx. 1,000 cases of 22 week and 3,000 cases of 23 week which are ready for analyses in relation with their outcomes up to 3 years of age.

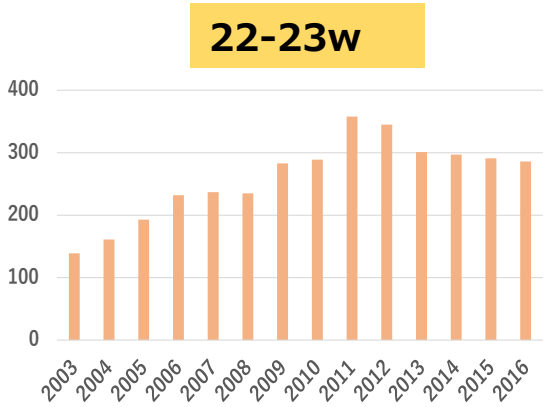
Study population/year NRNJ Database 2003-2016

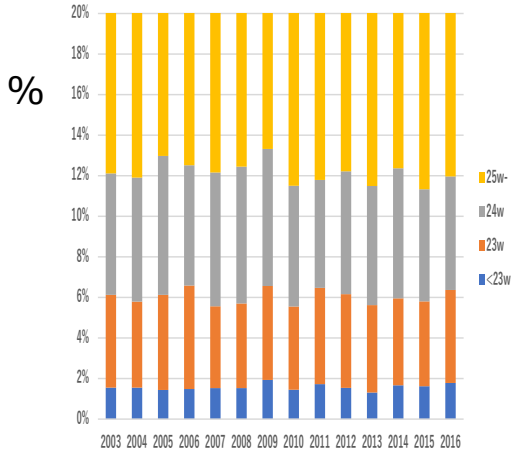
- The number of NICUs increased up to 2009 with Level 3 tertiary centers.
- Since 2010 Level 2 centers joined NRNJ and the number of NICUs doubled, with the increase of total N and decrease of cases/NICU(%).
- Number of 22-23w cases increased to 2011, then started to decrease.

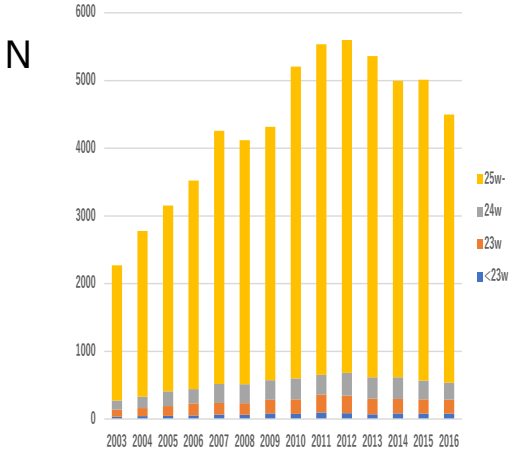
- The proportion of gestational groups were steady.

	22w	23w	24w	25w-	Infants Total	22+23w	N of NICUs	Infants /NICU
2003	35	104	136	1,995	2,270	139	40	57
2004	43	118	170	2,449	2,780	161	51	55
2005	45	148	216	2,744	3,153	193	63	50
2006	52	180	209	3,082	3,523	232	69	51
2007	65	172	281	3,741	4,259	237	89	48
2008	63	172	278	3,608	4,121	235	90	46
2009	83	200	292	3,741	4,316	283	98	44
2010	75	214	310	4,607	5,206	289	177	29
2011	95	263	295	4,885	5,538	358	218	25
2012	86	259	339	4,915	5,599	345	208	27
2013	70	231	315	4,745	5,361	301	190	28
2014	83	214	321	4,378	4,996	297	205	24
2015	81	210	277	4,444	5,012	291	169	30
2016	80	206	252	3,960	4,498	286	150	30
Total	956	2,691	3,691	53,294	60,632	3,647		





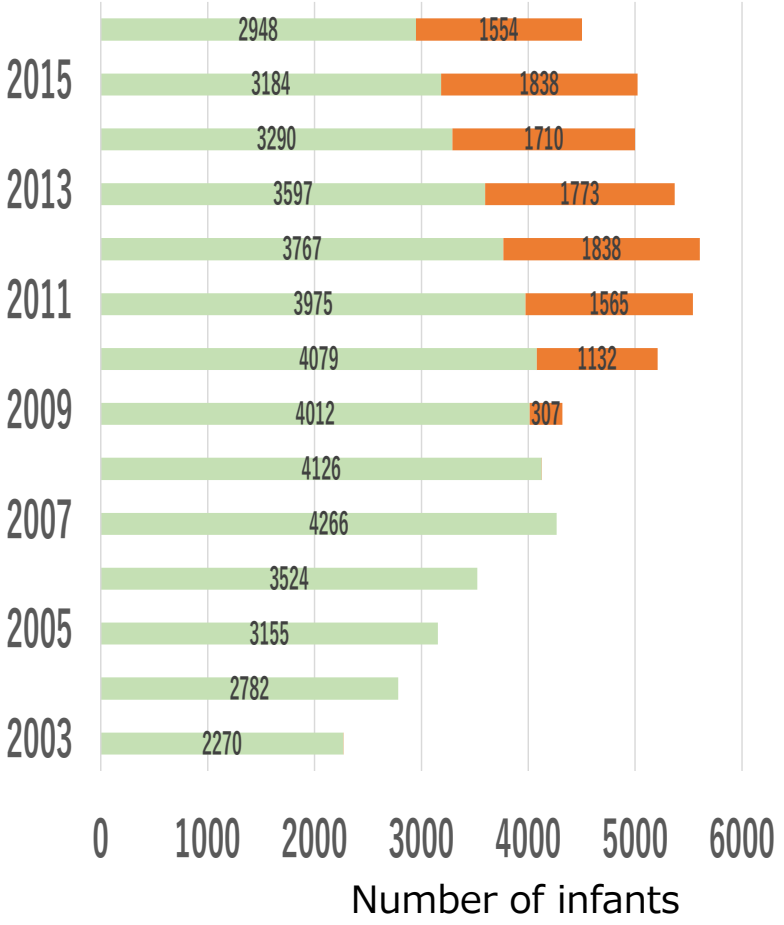




Dataset072297cat

Time of Participation to NRNJ (Early and Late NICUs)

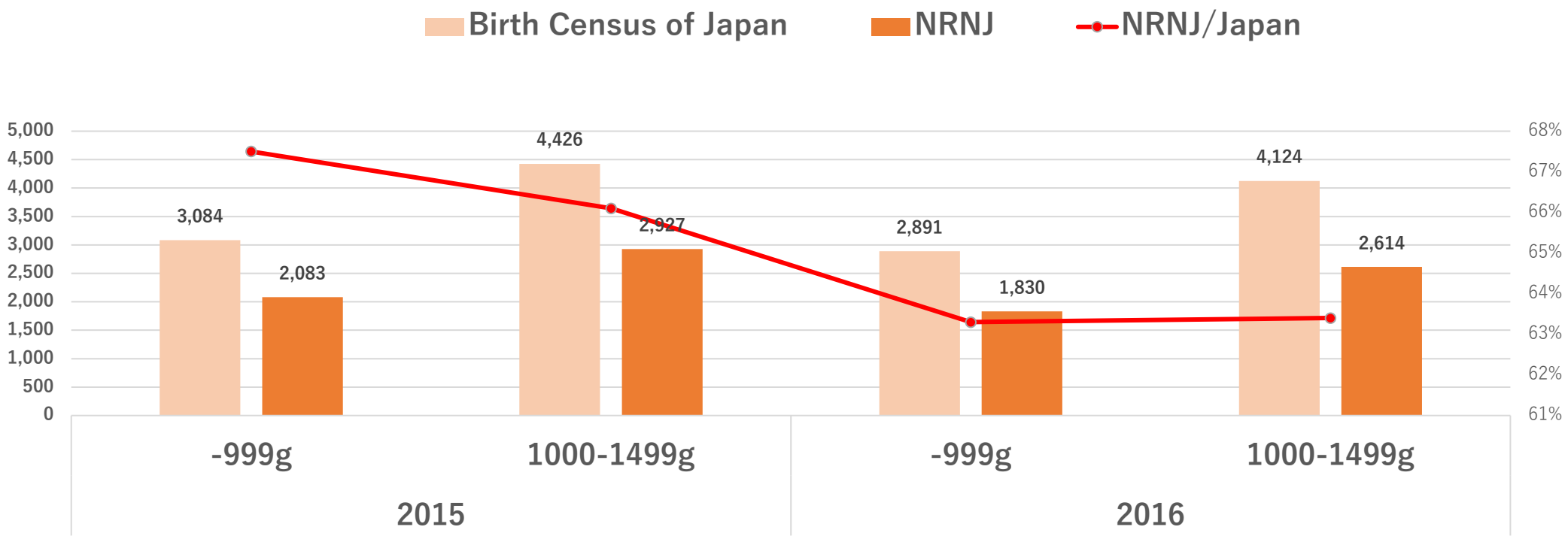
- Infants in NICUs of early participation to NRNJ(2003~2016) were 48,937 (80.7%), and late participation (2009~2016) were 11,707 (19.3%).
- The proportion of earlier gestation was smaller in Late NICUs.



N of infants	22-25w		26w-	
Early NICU	9,838	(20.1%)	39,099	(79.9%)
Late NICU	1,760	(15.0%)	9,947	(85.0%)

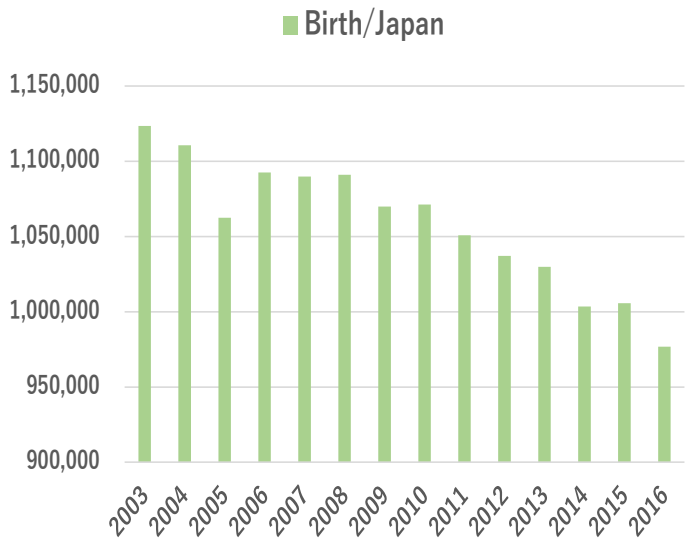
Birth Census of Japan vs NRNJ data-base

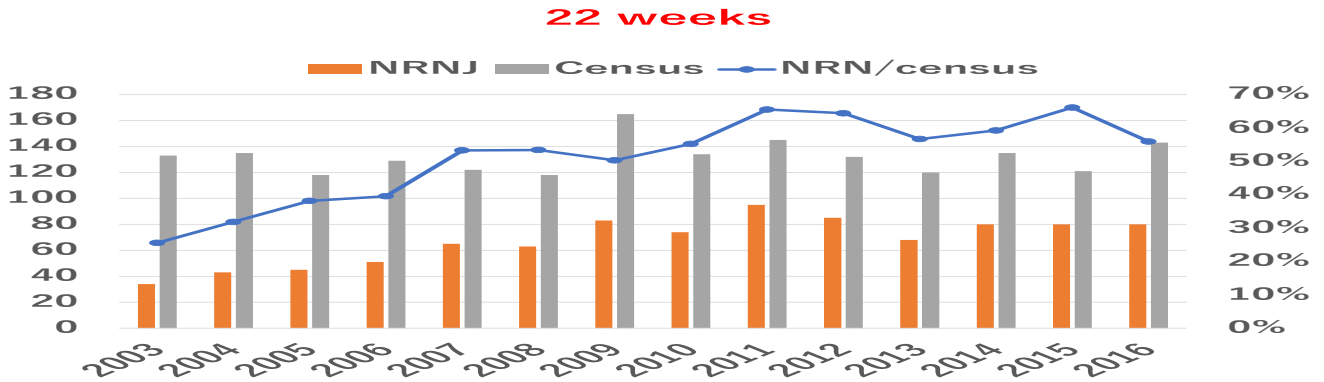
◆ NRNJ data-base was approximately 65% of very low birthweight infants of birth census born in 2015/2016

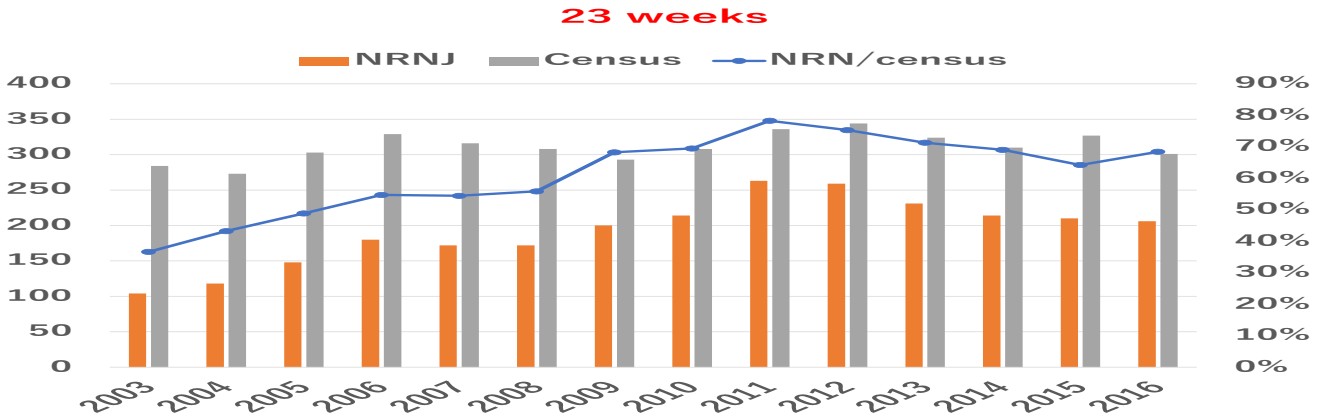


Annual trend of Birth Census Japan and NRNJ database

- Number of births were decreasing sharply since 2010.
- NRNJ database comprises 60%~70% census of Japan of 22 or 23 weeks.







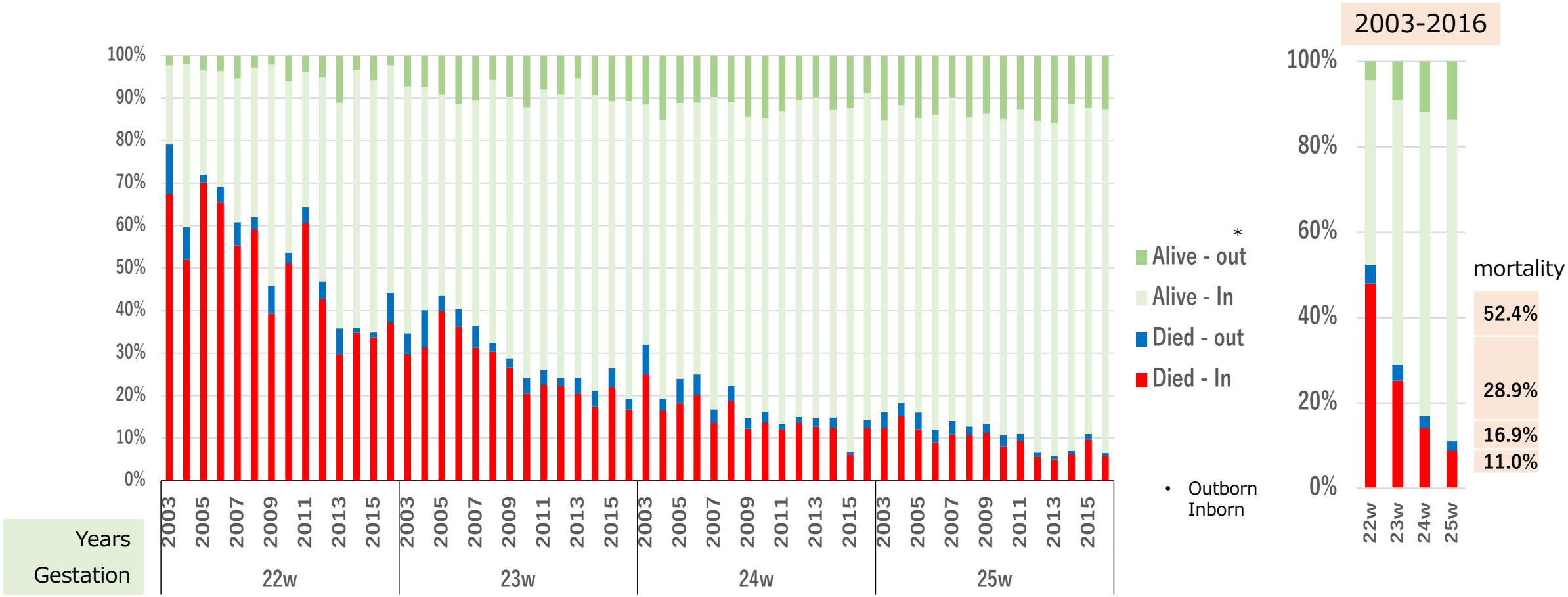
Summary
-Study Population-

1. NRNJ started in 2003 with 34 tertiary NICUs (Early). There were successive increase of NICUs every year, and level 2 NICUs (Late) joined since 2010.
2. NRNJ data-base is approximately 65% of very low birthweight infants of birth census born in 2015/2016.
3. In Japan number of births were decreasing sharply since 2010.
4. 22w and 23wker increased in number in NRNJ until 2011, then decreasing parallel to the number of birth.

Contents

Annual trend of mortality for 22w, 23w, 24w & 25w(In/Out born)

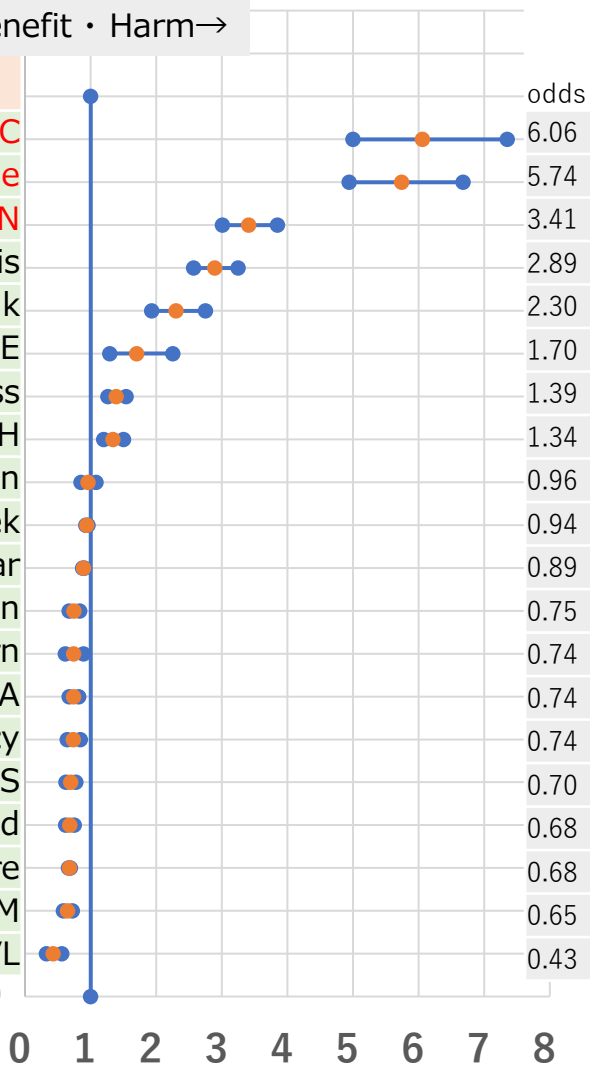
◆ In 14 years mortality nearly halved in each gestational groups.



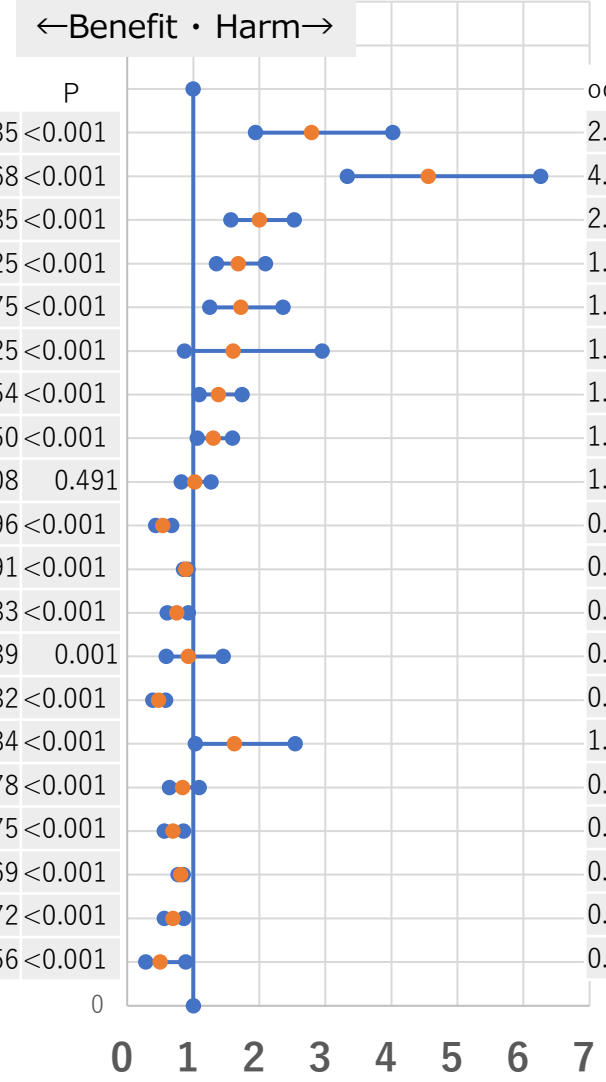
Perinatal factor for Death (comparing <1500g and 22-23w)

◆ Top three are NEC, pulmonary hemorrhage and PPHN both for <1500g and 22-23 weeks.

Death <1500



Death 22, 23w

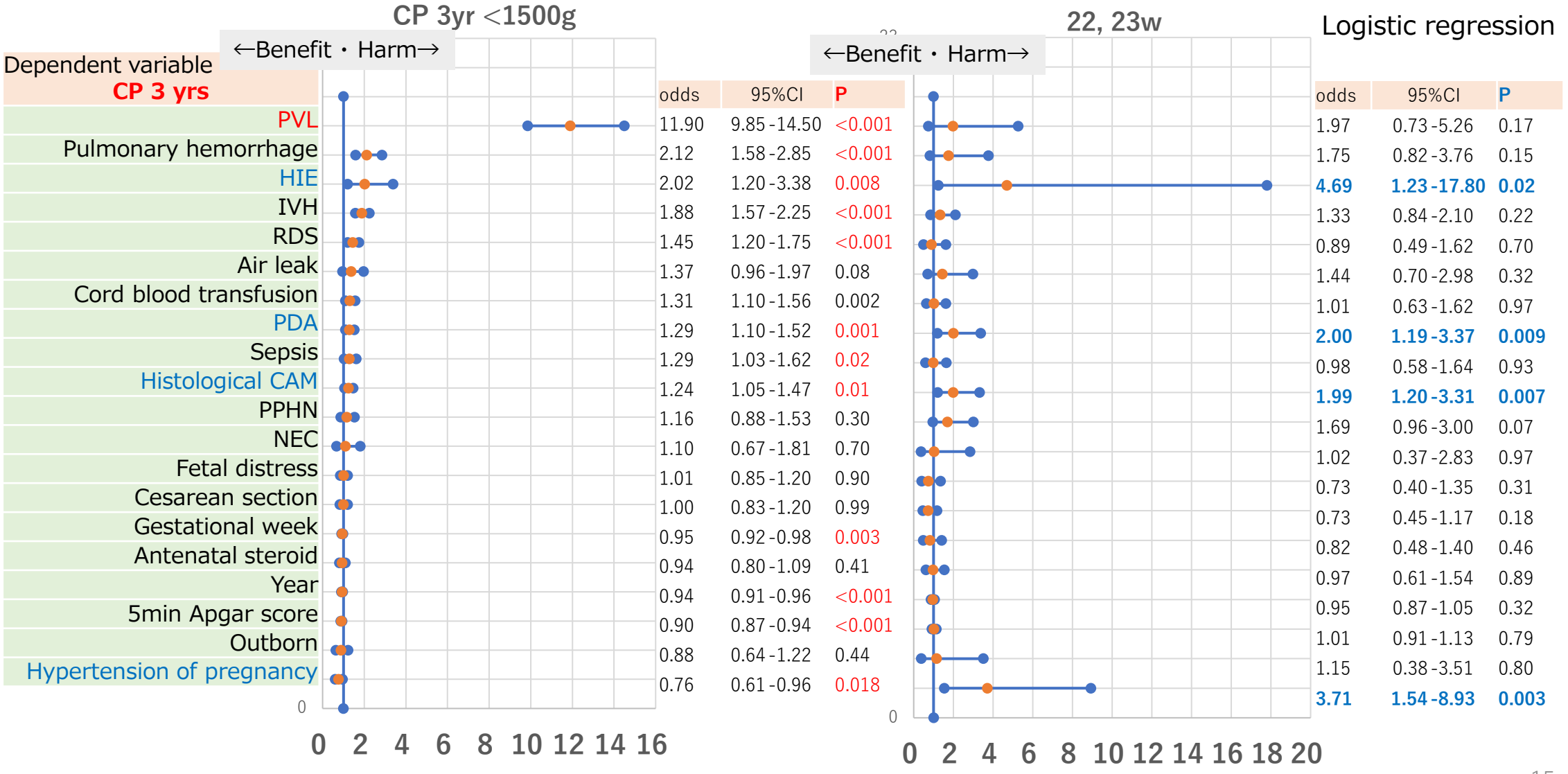


Logistic regression

Dependent variable **Death**	odds	95%CI		P	odds	95%CI		P
NEC	6.06	5.00	-7.35	<0.001	2.79	1.94	-4.02	<0.001
Pulmonary hemorrhage	5.74	4.94	-6.68	<0.001	4.56	3.33	-6.26	<0.001
PPHN	3.41	3.01	-3.85	<0.001	2.00	1.57	-2.53	<0.001
Sepsis	2.89	2.57	-3.25	<0.001	1.68	1.35	-2.09	<0.001
Air leak	2.30	1.93	-2.75	<0.001	1.72	1.25	-2.36	<0.001
HIE	1.70	1.29	-2.25	<0.001	1.60	0.87	-2.95	0.133
Fetal distress	1.39	1.26	-1.54	<0.001	1.38	1.09	-1.74	0.007
IVH	1.34	1.20	-1.50	<0.001	1.30	1.06	-1.59	0.011
Cord blood transfusion	0.96	0.85	-1.08	0.491	1.02	0.82	-1.27	0.873
Gestational week	0.94	0.93	-0.96	<0.001	0.54	0.43	-0.67	<0.001
Year	0.89	0.88	-0.91	<0.001	0.89	0.85	-0.92	<0.001
Cesarean section	0.75	0.67	-0.83	<0.001	0.75	0.60	-0.92	0.007
Outborn	0.74	0.61	-0.89	0.001	0.93	0.59	-1.45	0.733
PDA	0.74	0.67	-0.82	<0.001	0.47	0.39	-0.58	<0.001
Hypertension of pregnancy	0.74	0.64	-0.84	<0.001	1.62	1.03	-2.54	0.036
RDS	0.70	0.62	-0.78	<0.001	0.83	0.64	-1.09	0.191
Antenatal sterod	0.68	0.62	-0.75	<0.001	0.69	0.56	-0.85	<0.001
5min Apgar score	0.68	0.66	-0.69	<0.001	0.81	0.77	-0.84	<0.001
Histological CAM	0.65	0.58	-0.72	<0.001	0.69	0.56	-0.86	<0.001
PVL	0.43	0.32	-0.56	<0.001	0.50	0.28	-0.88	0.017

Perinatal factor for CP 3 yrs (comparing <1500g and 22-23w)

- PVL is the strongest factor for <1500g.
- For 22-23 weeks HIE, PDA, histological CAM and hypertension of pregnancy are significant factors.

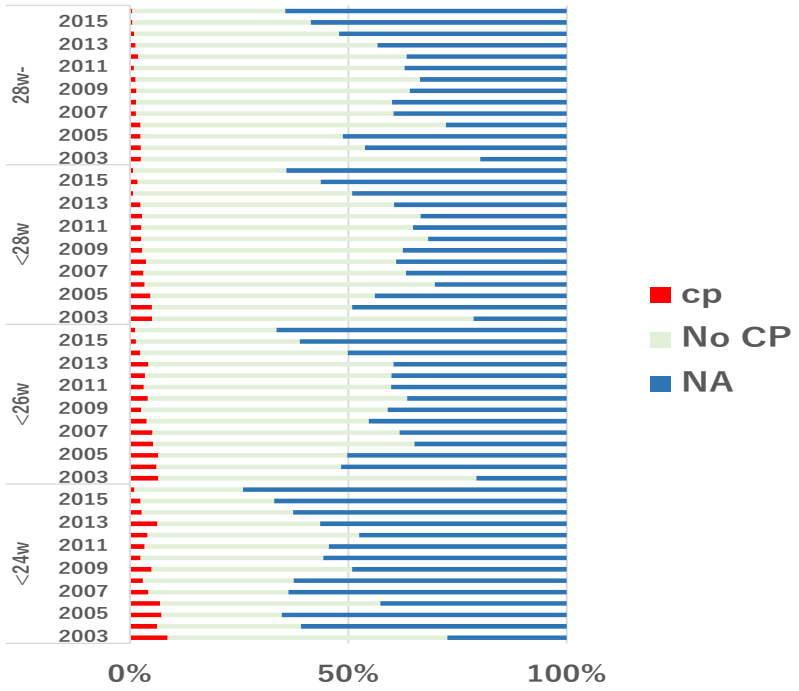


NRNJ Follow-up

- Each participating center registered the NICU and follow-up data.
- The follow-up were done by neonatologists and psychologists based on “Protocol for the multicenter follow-up study of VLBW infants in NICU-network database”, supported by Japan Neonatal Follow-up Study Group.
- The assessment was performed at a chronological age of 36–42 months. The developmental quotient (DQ) at 3 years was by chronological age. Cognitive functions were assessed using the Kyoto Scale of Psychological Development (KSPD) test*.
  (KSPD-DQ<70 is equivalent to Bayley III-DQ<85)

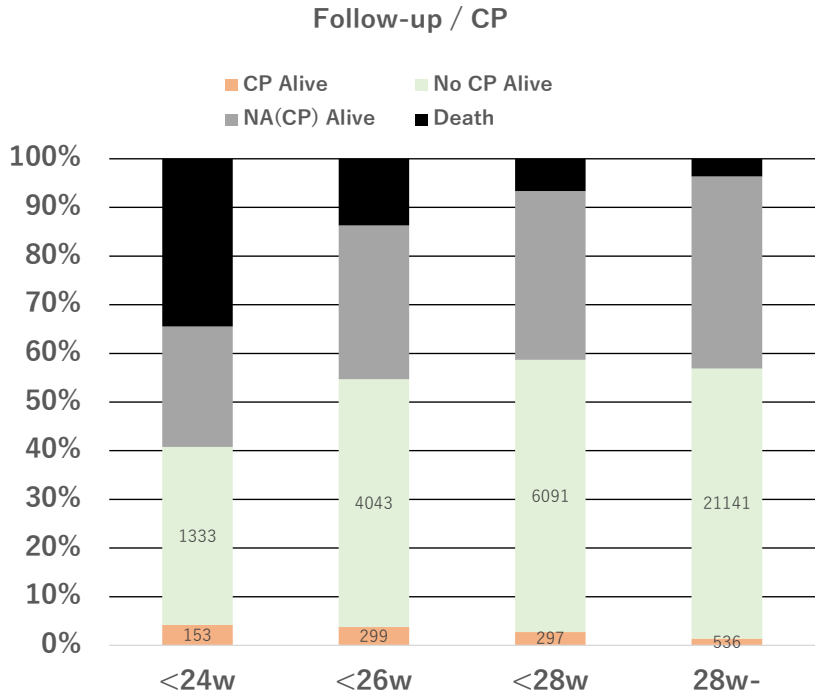
* Kono Y, Yonemoto N, Kusuda S, *et al*. Developmental assessment of VLBW infants at 18 months of age: a comparison study between KSPD and Bayley III. *Brain Dev* 2016;38:377–85.

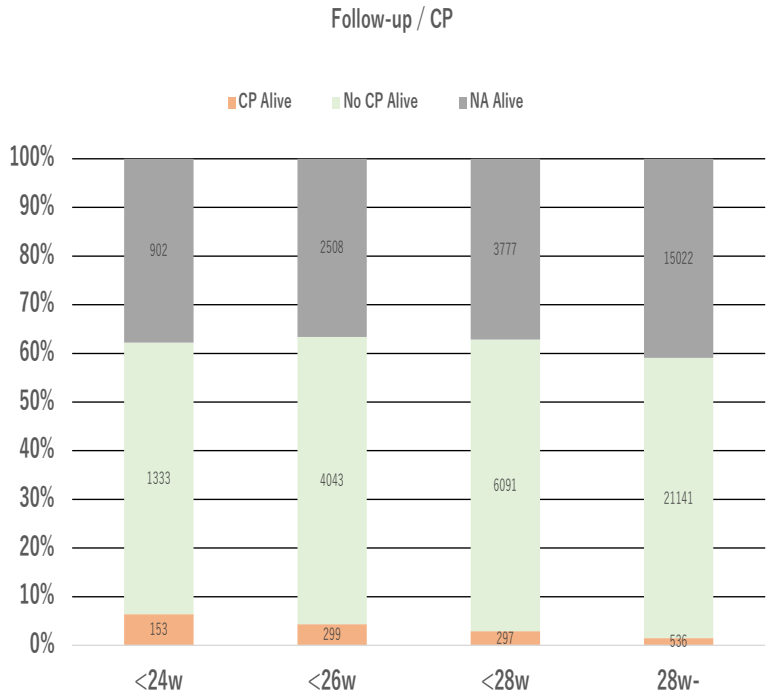
- A large proportion of infants “Not Available” has been a major limitation in NRNJ database.
- Percentage of NA increased, indicating the follow-up rate deteriorated.



Follow-up for cerebral palsy

◆ A large proportion of infants “Not Available” has been a major limitation in NRNJ database.

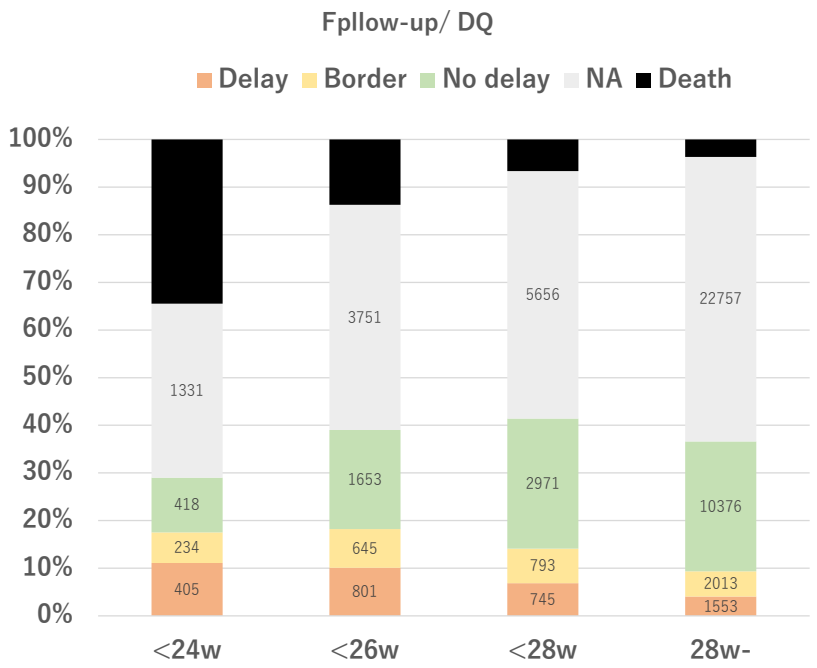


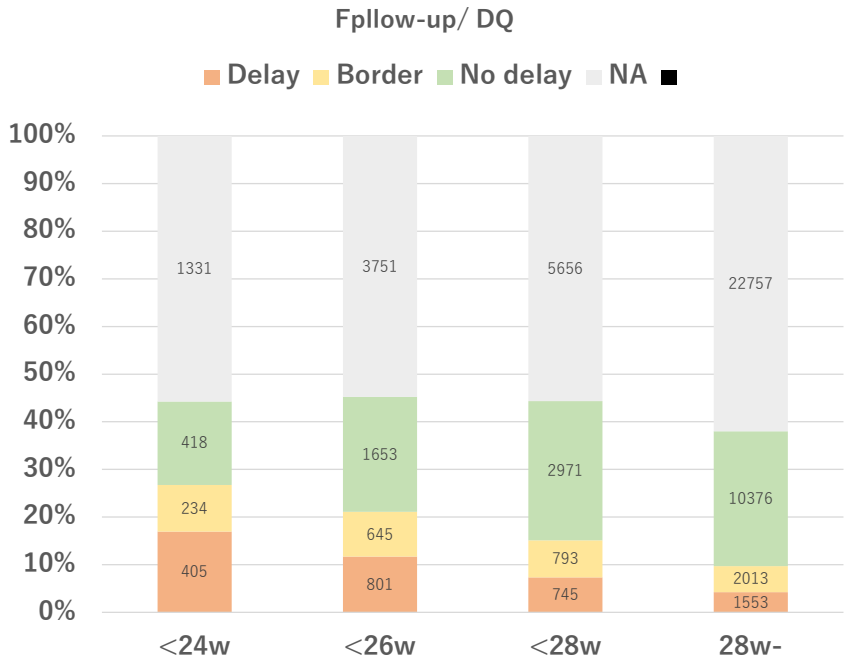


NA and Death categories will be excluded in the following analysis unless otherwise stated.

Follow-up for cognition

◆ A large proportion of infants “Not Available” has been a major limitation in NRNJ database.





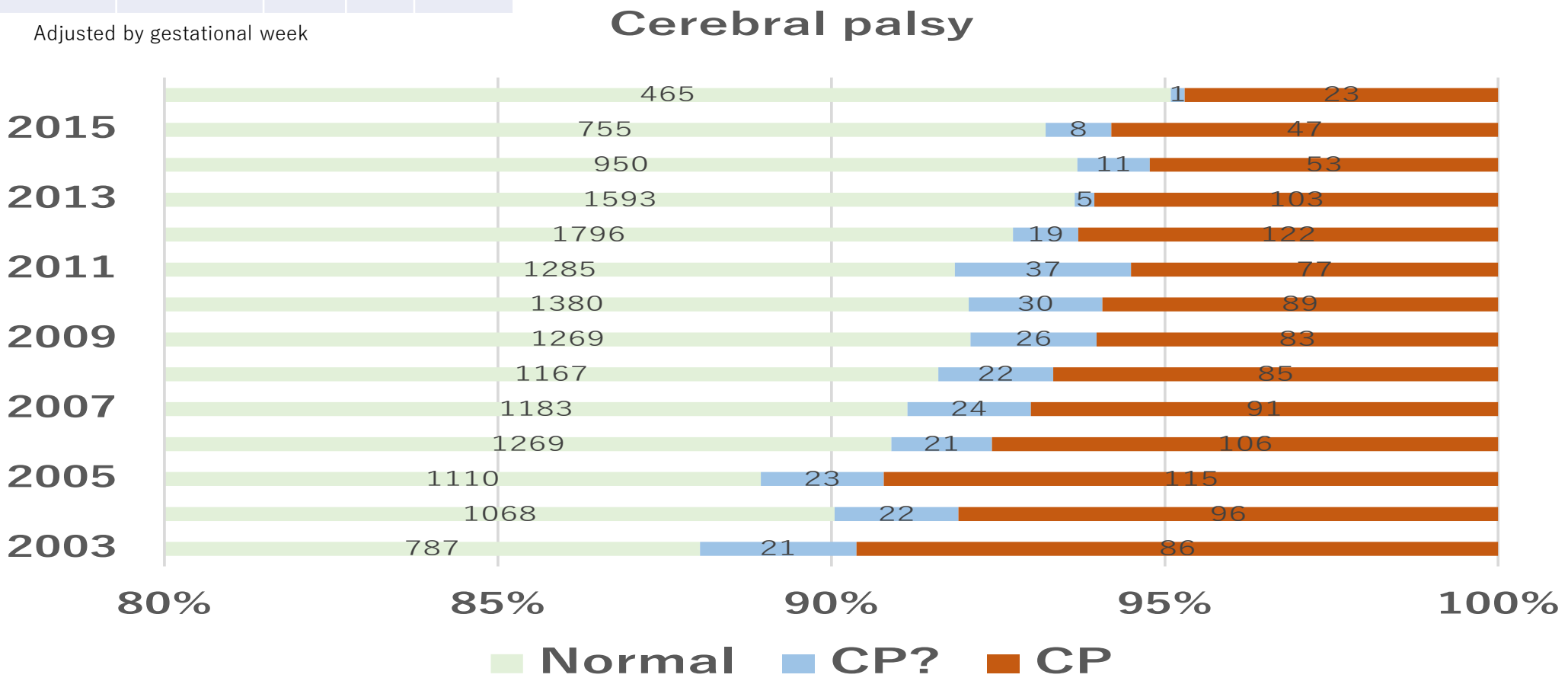
NA and Death categories will be excluded in the following analysis unless otherwise stated.

Cerebral Palsy

◆ The incidence of CP was decreasing.

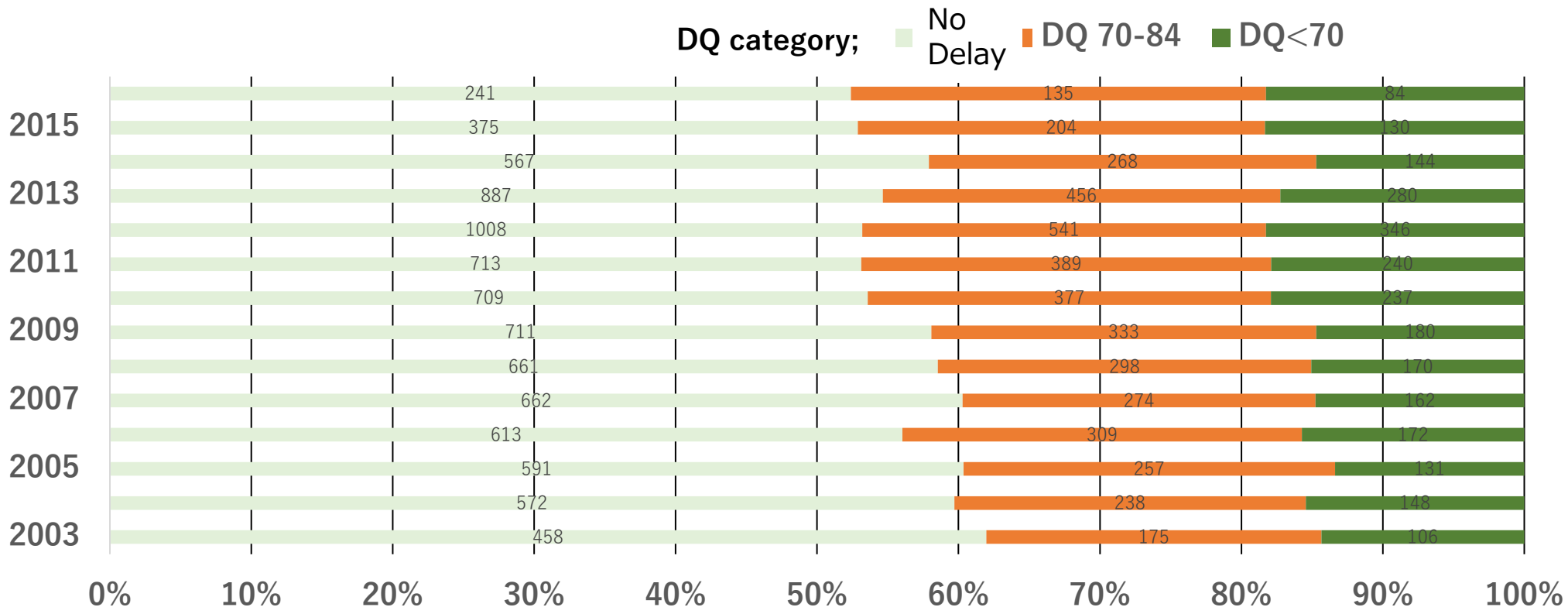
CP	odds ratio	95%CI	P
Year	0.92	0.91 -0.94	<0.001

Adjusted by gestational week



Cognitive Development

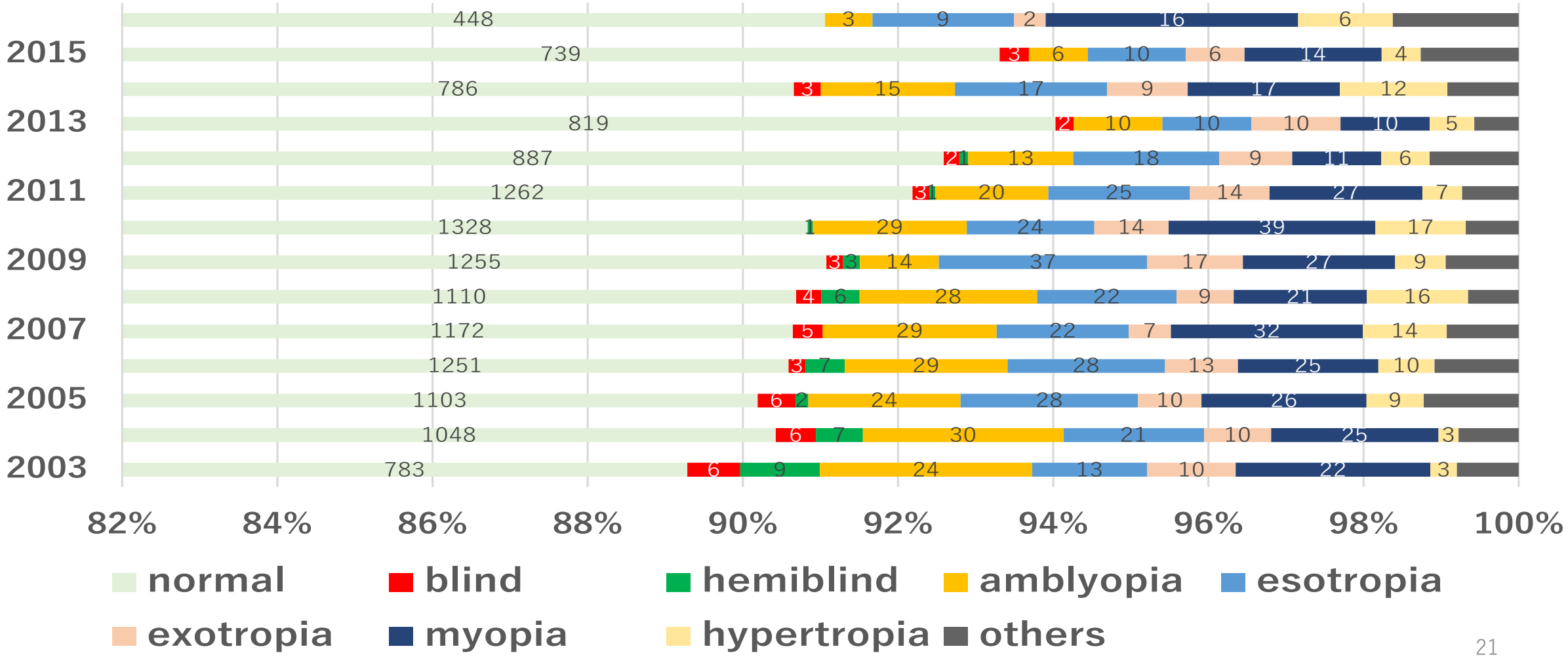
◆ Cognitive development showed no improvement.



A DQ score of KSPD <70, which represents a 70% achievement of standardized performance for the chronological age, was interpreted as significantly delayed according to the protocol by the Japan Neonatal Follow-up Study Group. A DQ score of KSPD <70 is equivalent to a Bayley III cognitive score <85.1

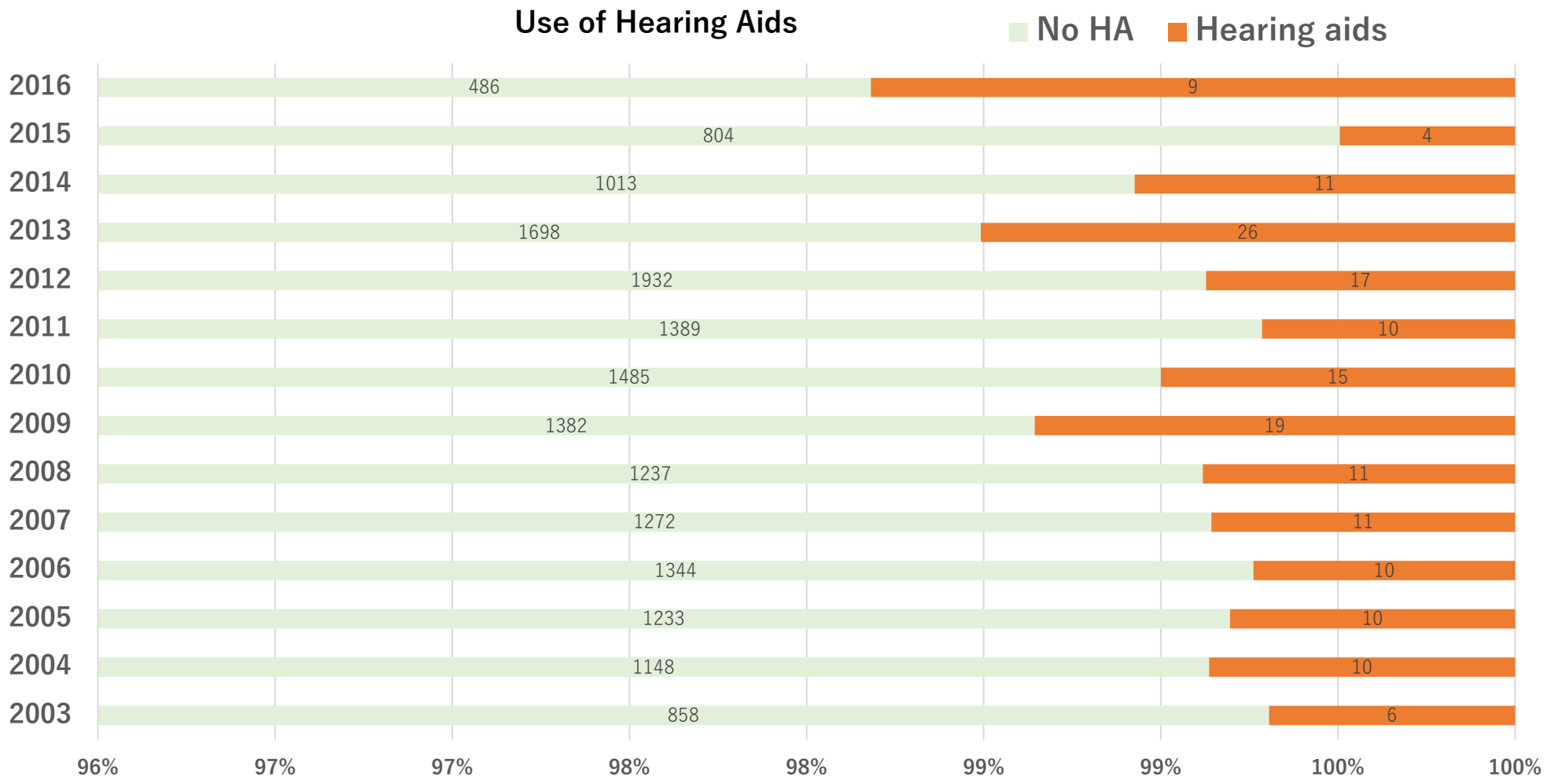
Visual Impairment

◆ Visual impairments decreased until 2013, then with some relapse?



Use of Hearing Aids

◆ Use of hearing aids remained within annual variation.



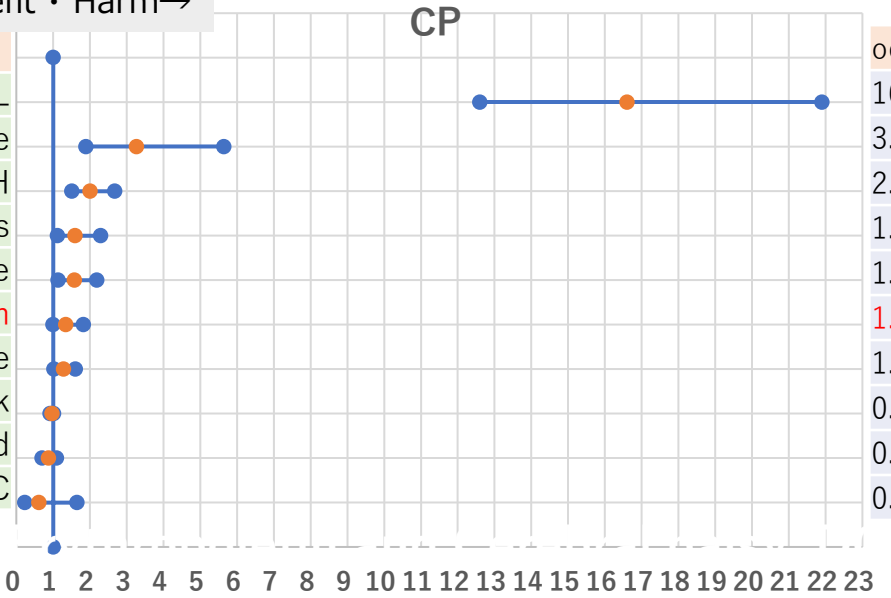
Erythropoietin and Cerebral palsy, DQ

Part of independent variables are selected .

	Died	Alive
EPO	435	12,490
22w	43	336
23w	92	1,277
24w	95	2,016
25w	82	2,411
26w	69	3,011
27w	54	3,439

Dependent variable
CP at 3 years

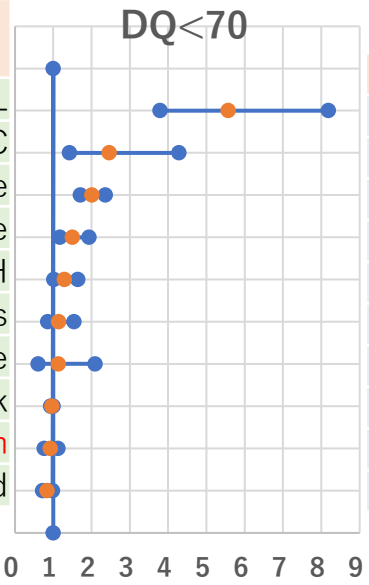
←Benefit・Harm→



Logistic regression

odds	95%CI		P
16.60	12.60	-21.9	<0.001
3.26	1.89	-5.64	<0.001
2.00	1.50	-2.67	<0.001
1.59	1.11	-2.29	0.012
1.57	1.13	-2.18	0.007
1.34	0.99	-1.82	0.06
1.28	1.02	-1.60	0.03
0.96	0.91	-1.01	0.10
0.87	0.69	-1.09	0.23
0.61	0.23	-1.64	0.32

Dependent variable
DQ at 3.years <70



odds	95%CI		P
5.57	3.79	-8.18	<0.001
2.46	1.42	-4.28	0.001
2.01	1.71	-2.36	<0.001
1.50	1.17	-1.93	0.001
1.29	1.01	-1.64	0.03
1.14	0.85	-1.54	0.39
1.13	0.61	-2.09	0.70
0.96	0.93	-1.00	0.025
0.92	0.76	-1.12	0.41
0.84	0.72	-0.98	0.02

◆ In NRNJ Database, use of erythropoietin (for erythropoiesis) showed no correlation either with cerebral palsy nor cognitive function at 3 years.

(Sandra E Juul , Bryan A Comstock , et al, A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants. N Engl J Med. 2020 Jan 16;382(3):233-243. doi: 10.1056/NEJMoa1907423. PENUT Trial 2013-2016)

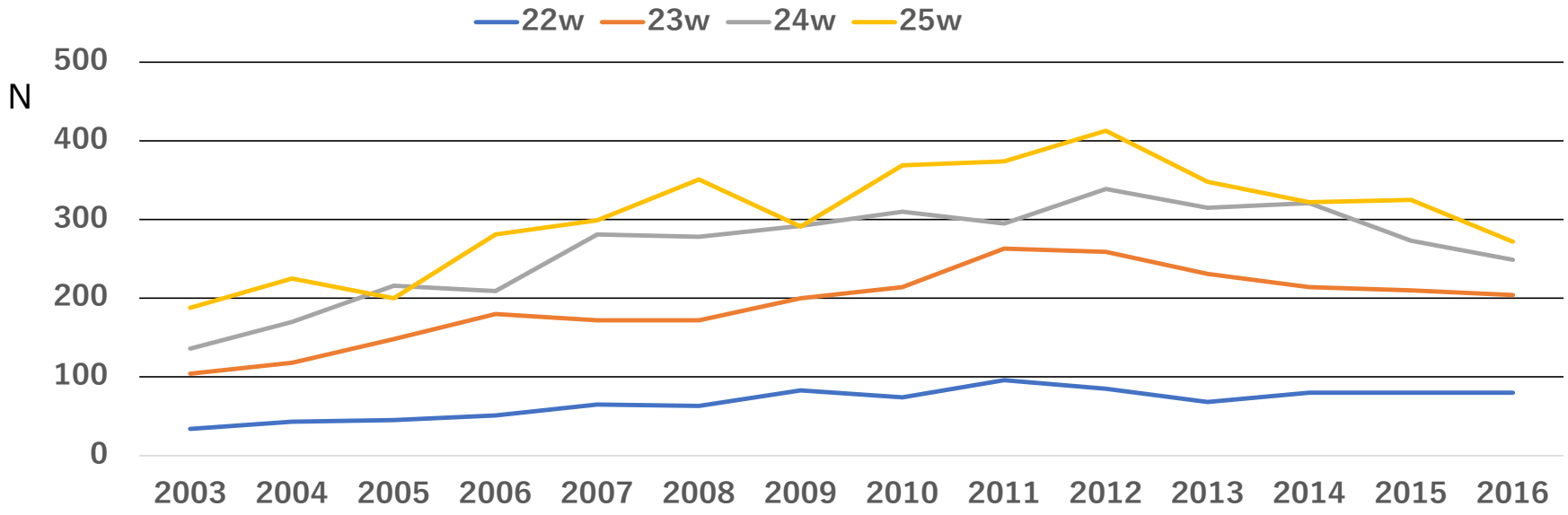
Summary
-mortality and impairment-

1. In 10 years (2003-2012) mortality nearly halved in each gestational groups.
2. Hypoxic ischemic encephalopathy, necrotizing enterocolitis, and pulmonary hemorrhage, are top three factors for “Cerebral palsy at 3 years or death” in <1500g and 22-23w
3. A large proportion of infants “No Available” has been a major limitation in NRNJ database.
4. The incidence of CP and visual impairments were decreasing.
5. Cognitive development shows no improvement.
6. Visual impairments decreased until 2013, then with some relapse?
7. Use of hearing aids remain variable.

Contents

Trend of Admission of 20w ~ 25w

◆ In 1996 amendment of maternity protection law (artificial abortion <24w → <22w).



Number of infants

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
20w	1							1			1	1	1		5
21w				1						1	1	3			6
22w	34	43	45	51	65	63	83	74	96	85	68	80	80	80	947
23w	104	118	148	180	172	172	200	214	263	259	231	214	210	204	2,689
24w	136	170	216	209	281	278	292	310	295	339	315	321	273	249	3,684
25w	188	225	200	281	299	351	291	369	374	413	348	322	325	272	4,258
Total	463	556	609	722	817	864	866	968	1,028	1,097	964	941	889	805	11,589

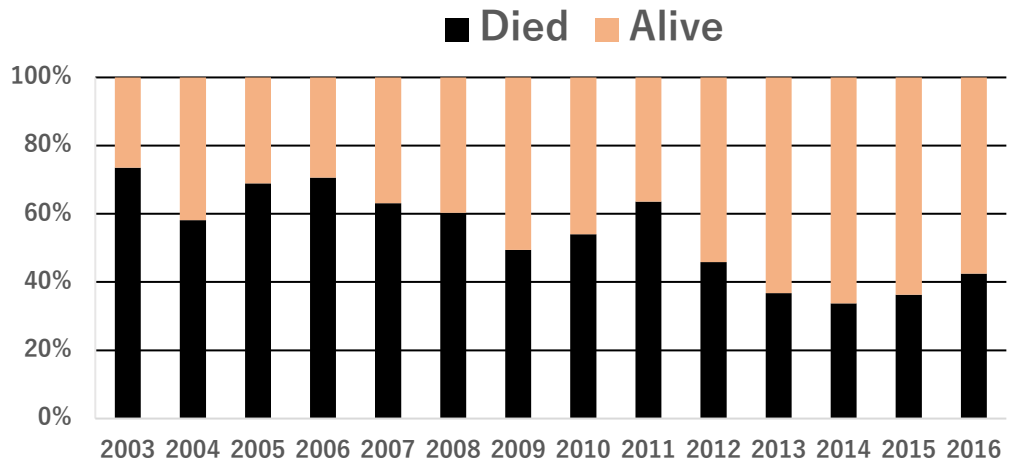
Cinderella effect

Mortality of 20w, 21w & 22w

- The mortality decreased 30% in 14 years for 22 wk.
- After 2011 the odds ratio of year for mortality was not significant i.e. no improvement

	20w					21w				22w												
	2003	2010	2013	2014	2015	2006	2012	2013	2014	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Died	1	1							2	25	25	31	36	41	38	41	40	61	39	25	27	29	34
Alive			1	1	1	1	1	1	1	9	18	14	15	24	25	42	34	35	46	43	53	51	46
Total	1	1	1	1	1	1	1	1	3	34	43	45	51	65	63	83	74	96	85	68	80	80	80
Mortality										**74%**	**58%**	**69%**	**71%**	**63%**	**60%**	**49%**	**54%**	**64%**	**46%**	**37%**	**34%**	**36%**	**43%**

22w



Dependent varialble :

Death	Odds	95%CI	P
Year	0.90	0.87-0.93	<0.001
Antenatal steroid	0.64	0.48-0.86	<0.01

Year>2011

Death	Odds	95%CI	P
Year	0.99	0.86-1.15	NS
Antenatal steroid	0.49	0.31-0.75	0.001

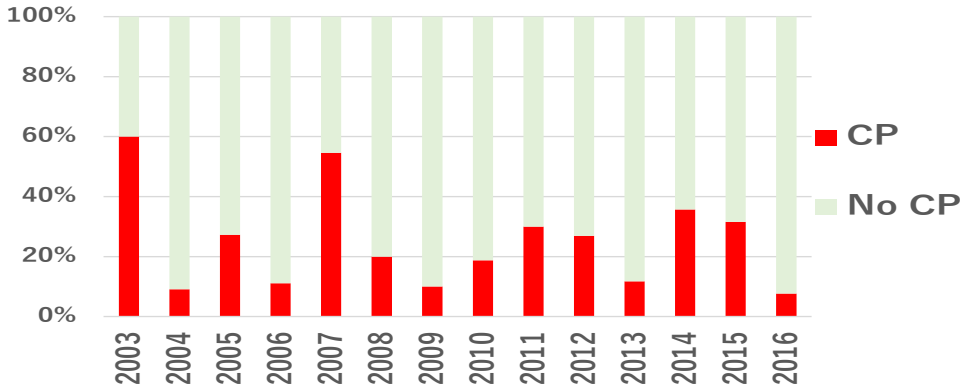
Logistic regression

CP & DQ<70 at 3 years
22 wk

◆ The CP rate for 22 week decreased (NS). The rate of DQ<70 increased (NS).

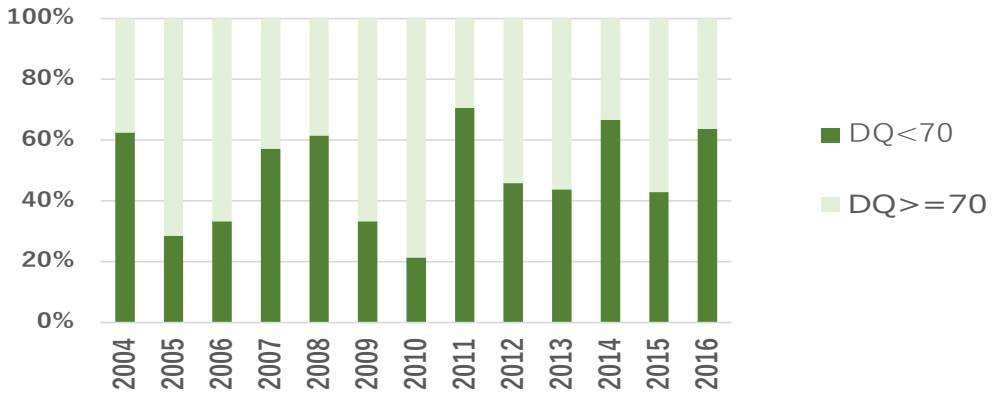
Dependent var. CP	odds	95%CI	
Year	0.99	0.9	-1.09

Logistic regression



DQ<70	odds	95%CI	
Year	1.06	0.95	-1.17

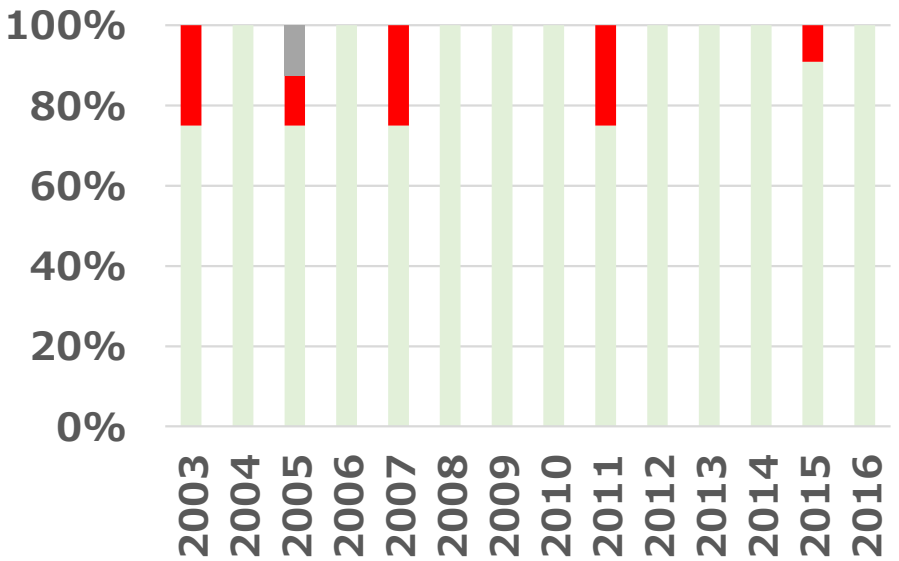
Logistic regression



Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
CP	3	1	3	1	6	3	2	3	6	7	2	5	6	1
No CP	2	10	8	8	5	12	18	13	14	19	15	9	13	12
Total	5	11	11	9	11	15	20	16	20	26	17	14	19	13
%CP	60.0%	9.1%	27.3%	11.1%	54.5%	20.0%	10.0%	18.8%	30.0%	26.9%	11.8%	35.7%	31.6%	7.7%
DQ<70	0	5	2	2	4	8	6	3	12	11	7	8	6	7
DQ>=70	0	3	5	4	3	5	12	11	5	13	9	4	8	4
Total	0	8	7	6	7	13	18	14	17	24	16	12	14	11
%DQ<70	–	62.5%	28.6%	33.3%	57.1%	61.5%	33.3%	21.4%	70.6%	45.8%	43.8%	66.7%	42.9%	63.6%

Visual impairment at 3 years
22 wk

◆ Blindness significantly decreased.



22w
3Y

Hemiblind
Blind
Normal

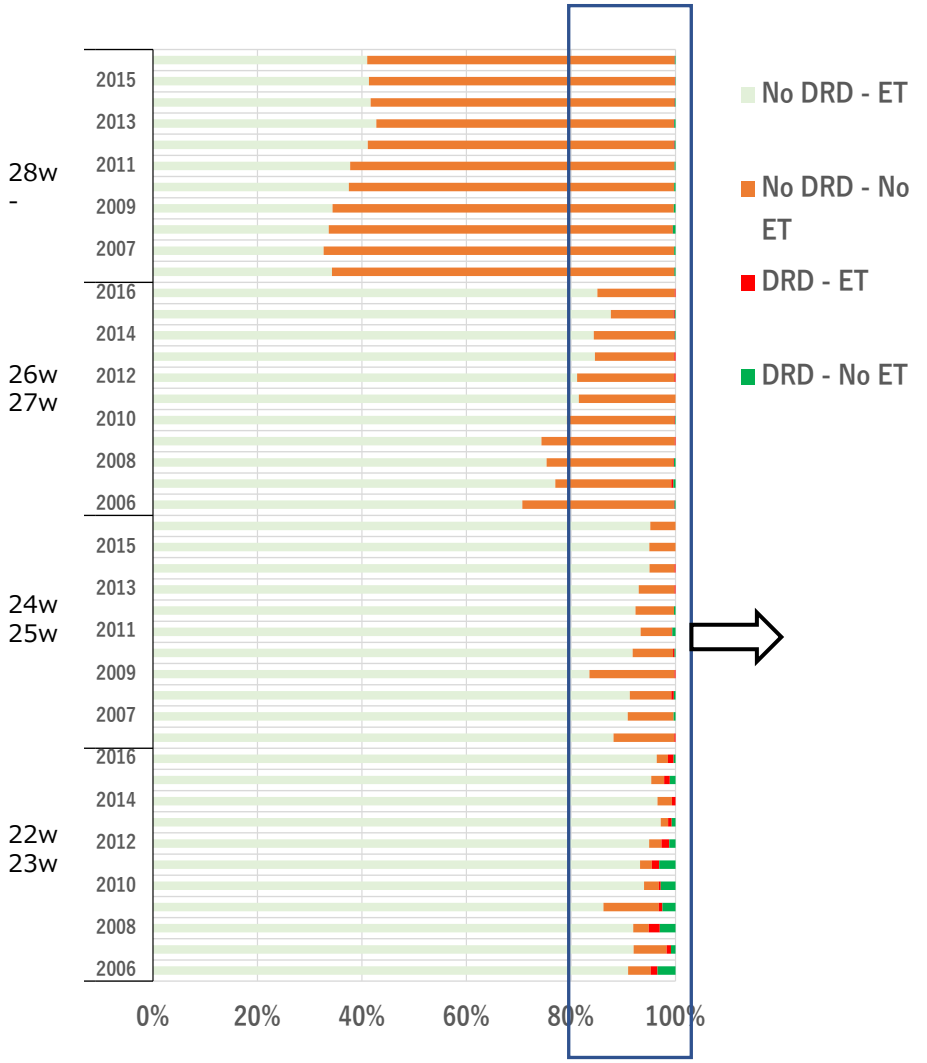
Depandent valiable 22w Blindness	odds	95%CI		P
Year	0.723	0.523	−1.000	<0.05

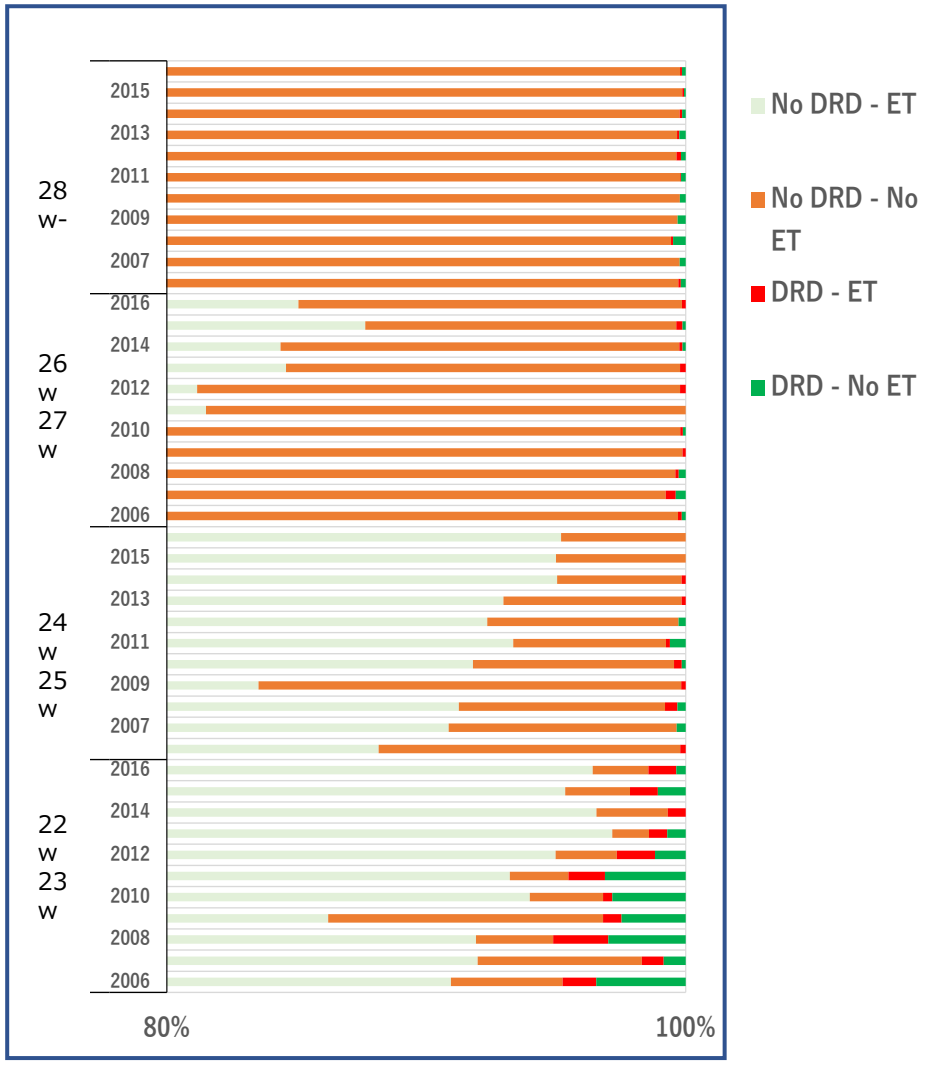
Logistic regression

22w	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Normal	3	8	6	5	3	4	6	5	3	5	7	3	10	3
Bi-lateral blind	1		1		1				1				1	
Hemi-lateral blind			1											
Total	4	8	8	5	4	4	6	5	4	5	7	3	11	3

Relations of Delivery room death/ Endotracheal intubation / Gestational weeks

- Majority are ○ “No DR death– ET” (increase) and ○“No DR death– No ET”(decrease).
- Rate of ● “ DR death – ET” and ●“DR death – No ET” are larger in infants 22~23 weeks than infants>23w, and this proportions decreased toward 2016.





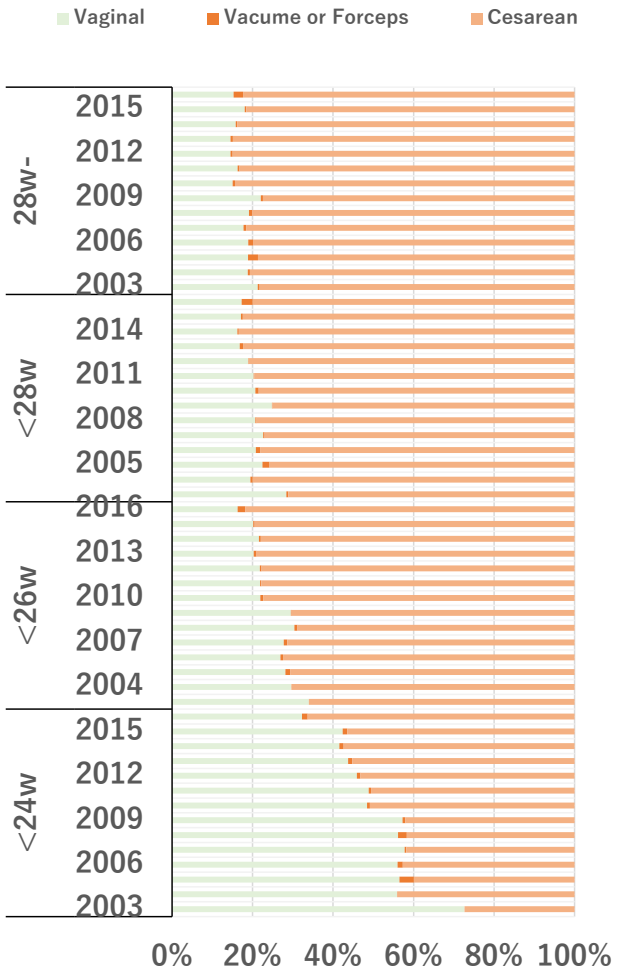
Summary
-22 week-

1. In 2003~2016 there were small increased rate of 22 & 23 wks gestation.
2. The mortality decreased 30% in 14 years for 22 week. After 2011 the odds ratio of year for mortality was not significant i.e. no improvement
3. The CP rate for 22 week decreased (not significant).
4. The rate of DQ<70 increased (not significant).
5. Blindness significantly decreased.
6. Delivery room death rate of 22, 23w started to decrease since 2012

Contents

Mode of Delivery

◆ Increase of Cesarean section for 22w and 23w.



◆ ≧24w

Odds ratio for Cesarean section was 1.03/year and 1.07/gest. week

Subset: ≧24w

Dependent var. C/section	odds	95%CI	P
Year	1.03	1.03-1.04	<0.001
Gest. week	1.07	1.06-1.08	<0.001

◆ 22, 23w

Odds ratio for Cesarean section was 1.10/year and 3.12/gest. week

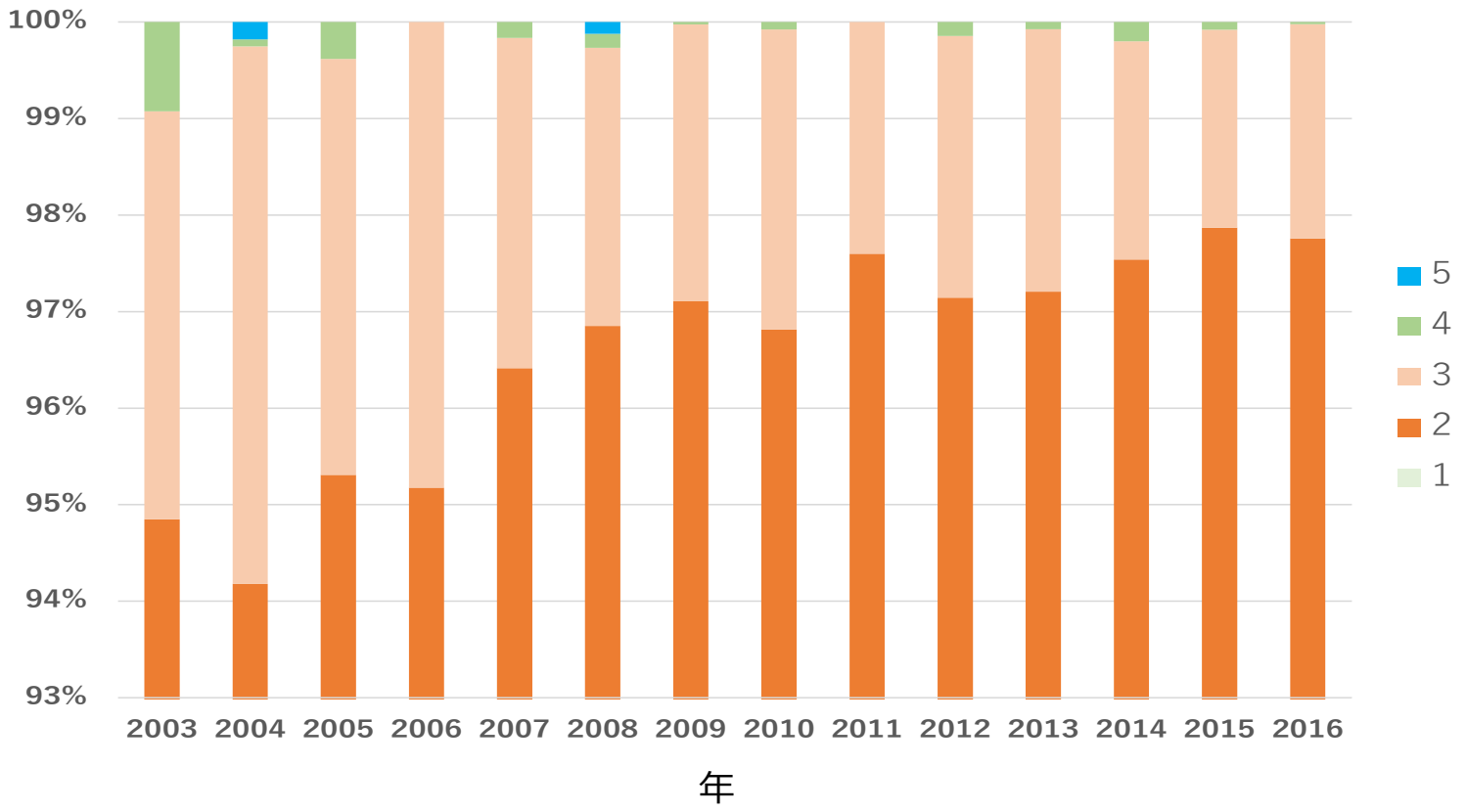
Subset: 22, 23w

C/section	odds	95%CI	P
Year	1.10	1.08-1.12	<0.001
Gest. Week	3.12	2.66-3.67	<0.001

Logistic regression

Multiple Pregnancy

- Triplets, Quads, Quins decreased by 2011.
- Triplets were still born approx. 2%, and Quads occasionally are seen.



Contents

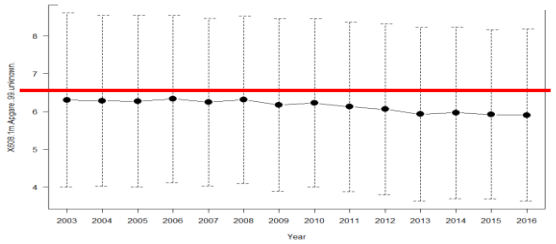
1 min & 5 min Apgar Scores

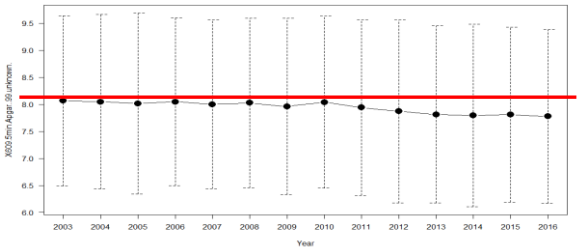
◆ 1 min & 5 min Apgar Scores declined after Level 2 & 3 NICUs merged in 2010.

1 min Apgar Score

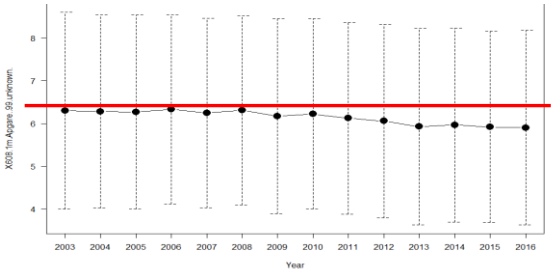
5 min Apgar Score

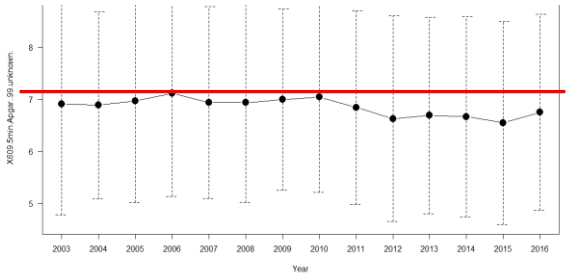
28w-



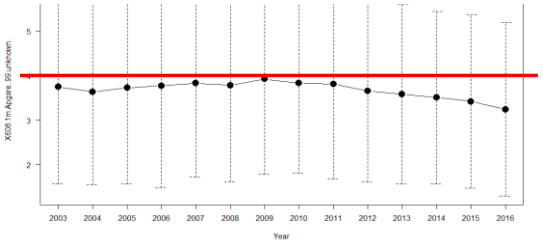


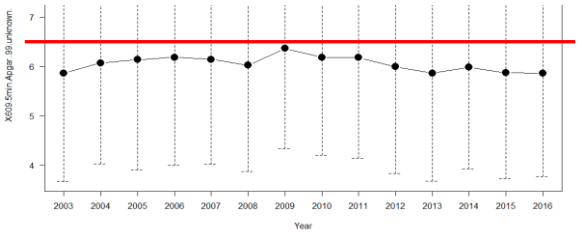
26w
27w



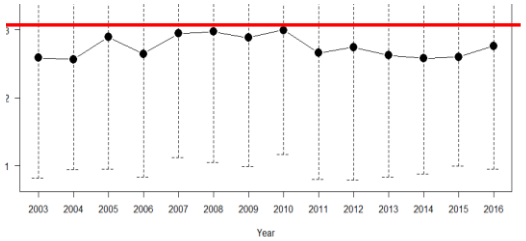


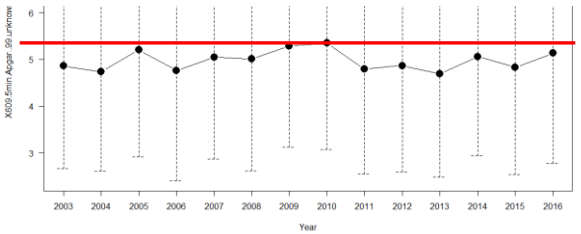
24w
25w





22w
23w





NICU category Late had odds ratio 1.08 (Early=1).

Dependent variable **5 min Apgar Score <4 (Asphyxia)**				
NICU Early=1	odds	95%CI		P
Gestation week	0.74	0.73	0.75	<0.001
Year	1.02	1.01	1.02	<0.001
NICU Late	1.08	1.02	1.16	0.013

Logistic regression

Acute Respiratory Disorders

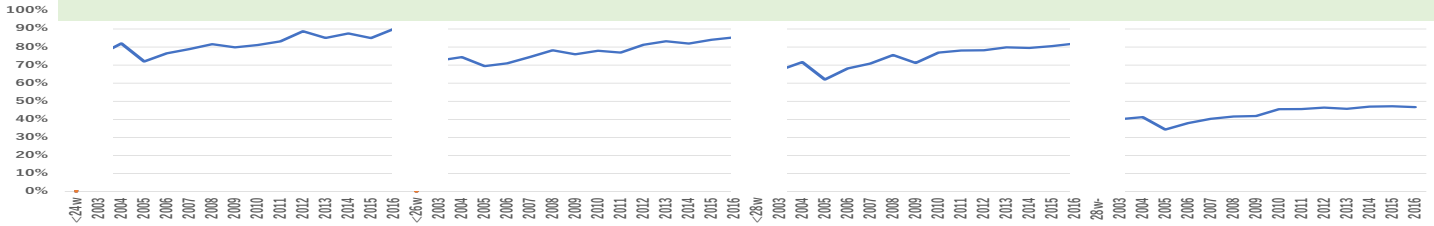
22, 23w　24, 25w　26, 27w　28w-

Dependent var.: RDS	odds	95%CI		P
Gest. week	0.704	0.699	0.709	<0.001
Year	1.050	1.050	1.060	<0.001

Logistic regression

RDS increased

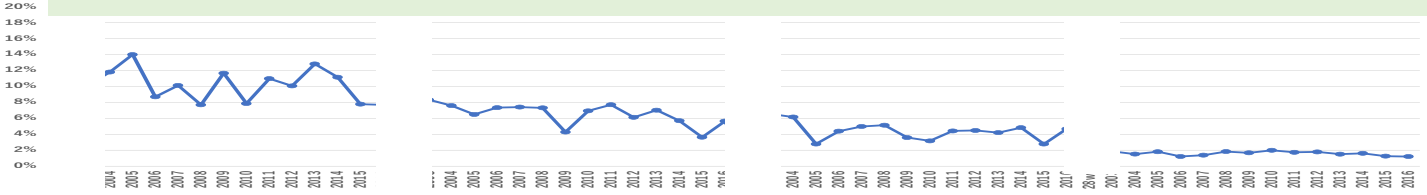
why RDS increased?



Pulmonary Hemorrhage	odds	95%CI		P
Gest. week	0.818	0.804	0.832	<0.001
Year	0.970	0.958	0.982	<0.001
RDS	3.060	2.670	3.510	<0.001

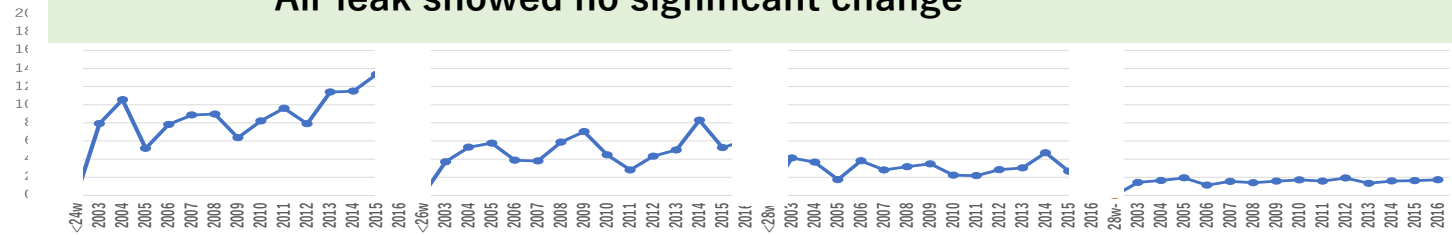
Pulmonary hemorrhage decreased

Why Pulmonary Hemorrhage decreased ?



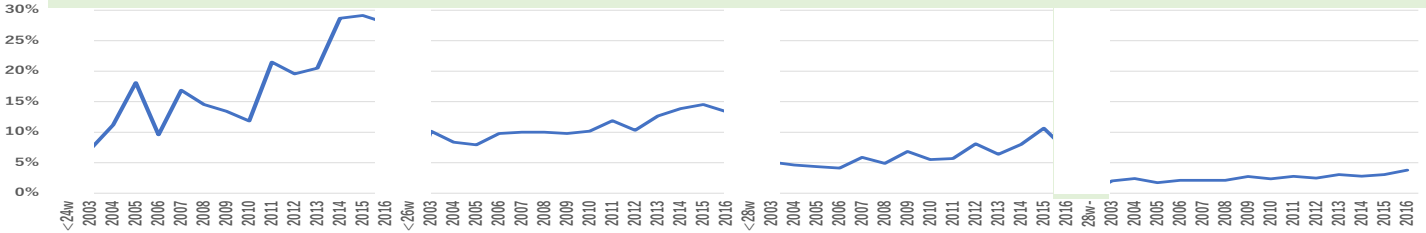
Air Leak	odds	95%CI		P
Gest. week	0.836	0.821	0.852	<0.001
Year	1.010	0.998	1.020	NS
RDS	1.810	1.600	2.060	<0.001

Air leak showed no significant change



PPHN	odds	95%CI		P
Gest. week	0.781	0.770	0.791	<0.001
Year	1.060	1.050	1.070	<0.001
RDS	1.420	1.300	1.560	<0.001

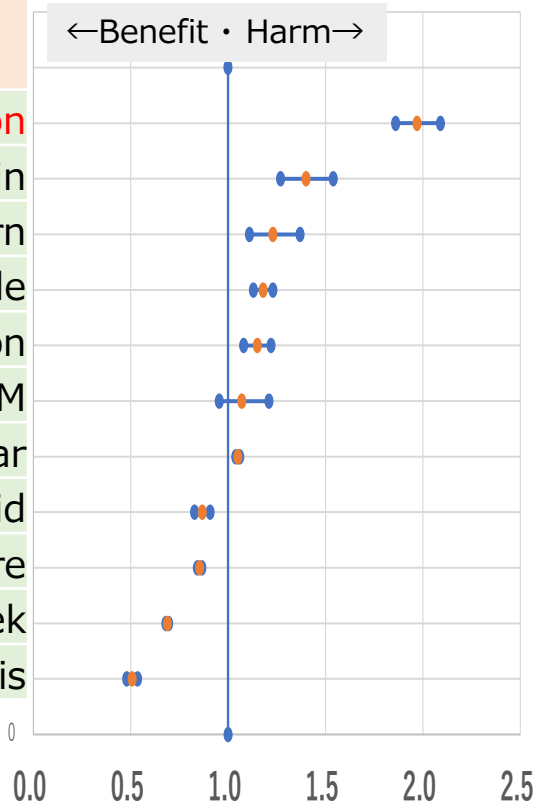
PPHN increased



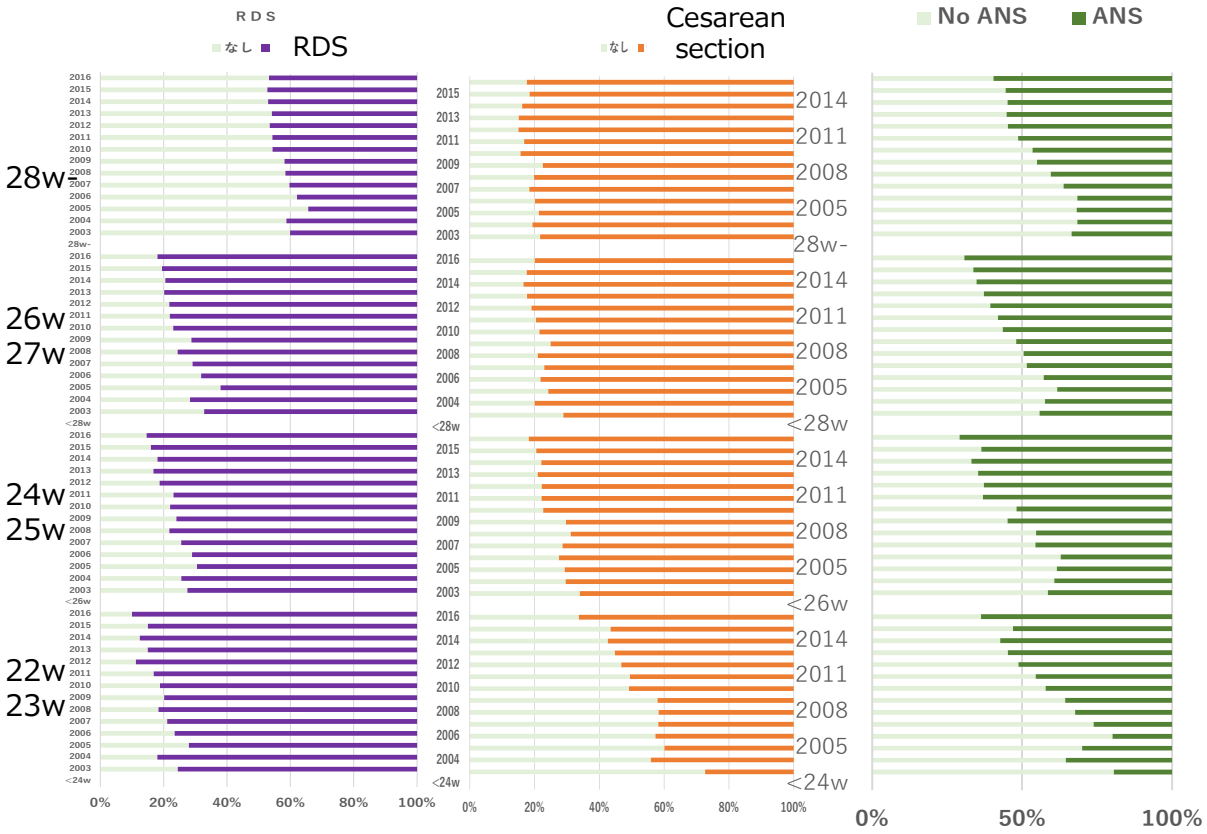
Why RDS increased ?

◆ The main reason of increasing RDS may be correlated increase of Cesarean section adjusted with antenatal steroid.

Dependent variable: RDS
Cesarean section
Prophylactic Indomethacin
outborn
male
Cord blood transfusion
Gestational DM
Year
Antenatal steroid
5 min Apgar score
Gestational week
Histological chorioamnionitis



Logistic regression

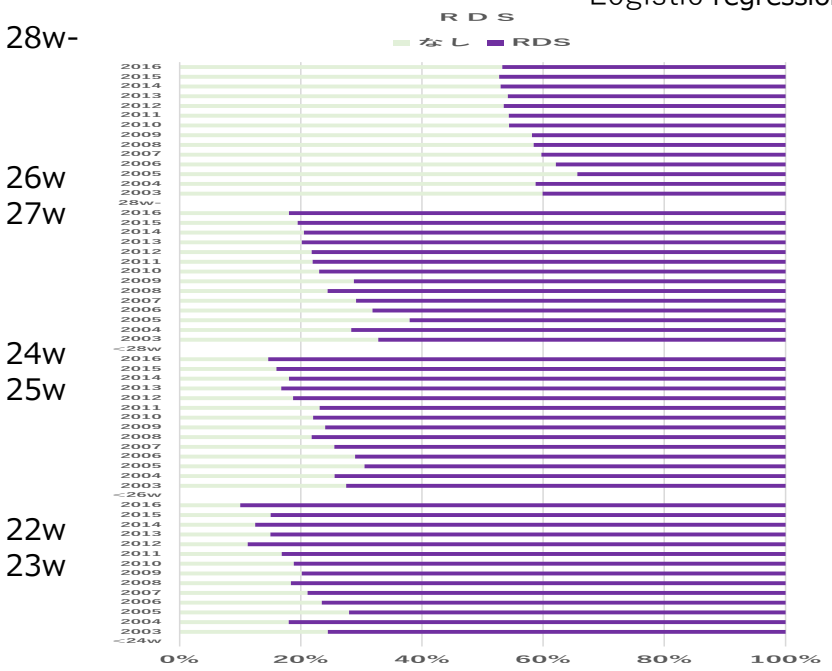


Why Pulmonary Hemorrhage decreased ?

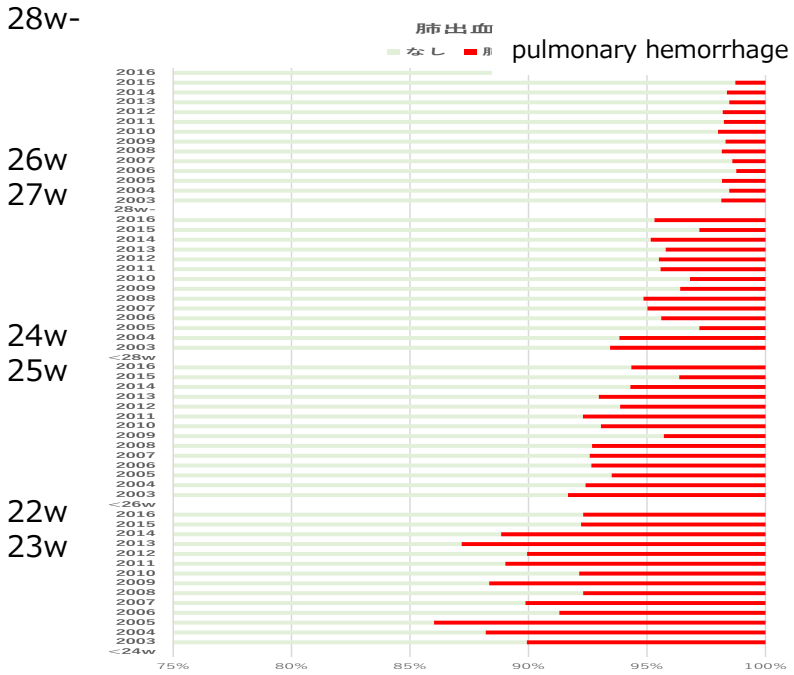
- In the textbook “pulmonary hemorrhage correlates with RDS” .
- Why pulmonary hemorrhage decreased with RDS increasing?

Dependent var. RDS	Odds	95%CI	P
Year	1.05	1.05 - 1.06	＜0.001
Gestation(w)	0.70	0.70 - 0.71	＜0.001

Logistic regression

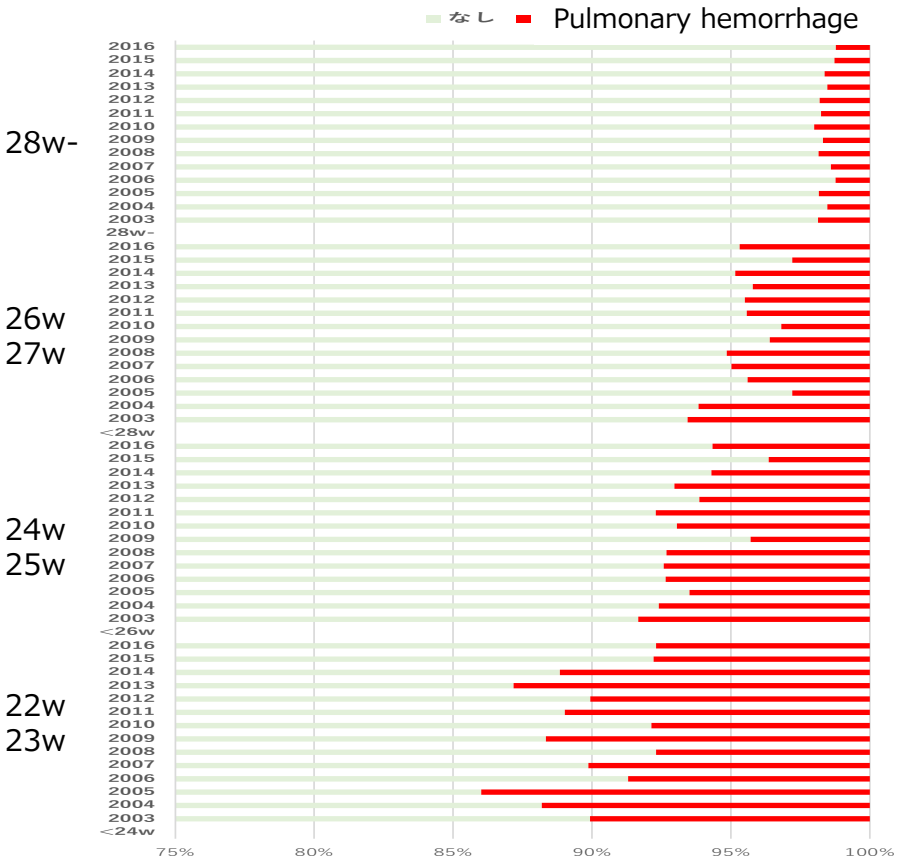


Pulmonary hemorrhage	Odds	95%CI	P
Gestation(w)	0.82	0.80 - 0.83	<0.001
Year	0.97	0.96 - 0.98	<0.001
RDS	3.06	2.67 - 3.51	<0.001

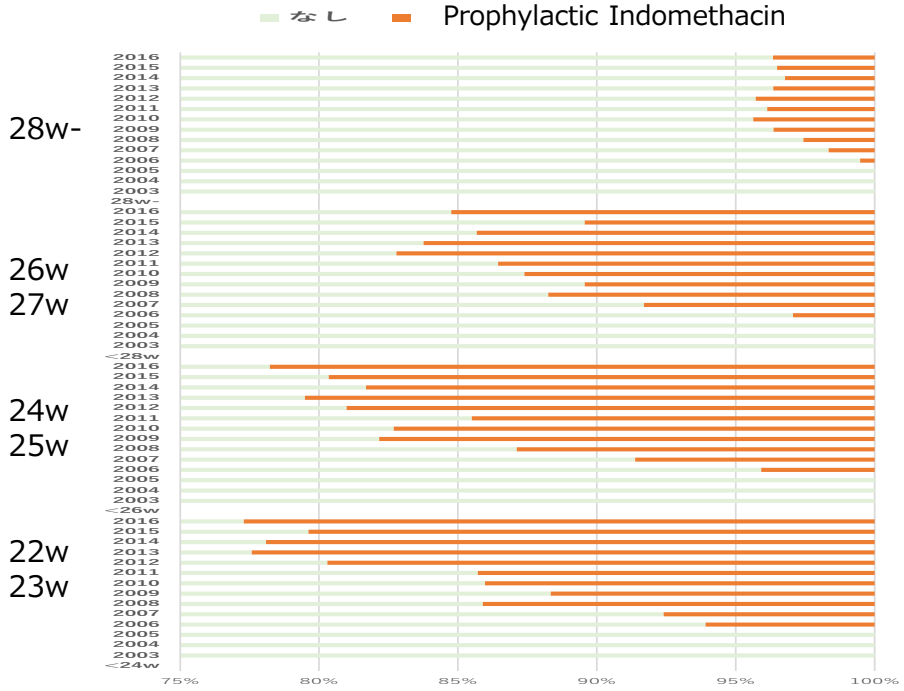


Why Pulmonary Hemorrhage decreased with RDS increasing ?

◆ The answer will be increasing administration of prophylactic Indomethacin.



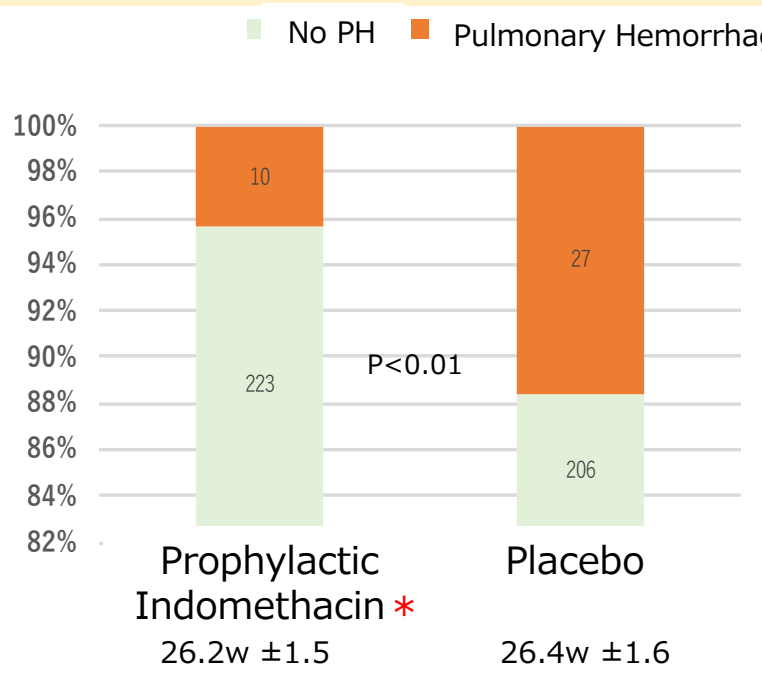
Dependent var. Prophylactic IND	Odds	95%CI		P
Gestation(w)	0.77	0.76	0.78	<0.001
Year	1.15	1.14	1.17	<0.001
RDS	1.82	1.66	1.99	<0.001



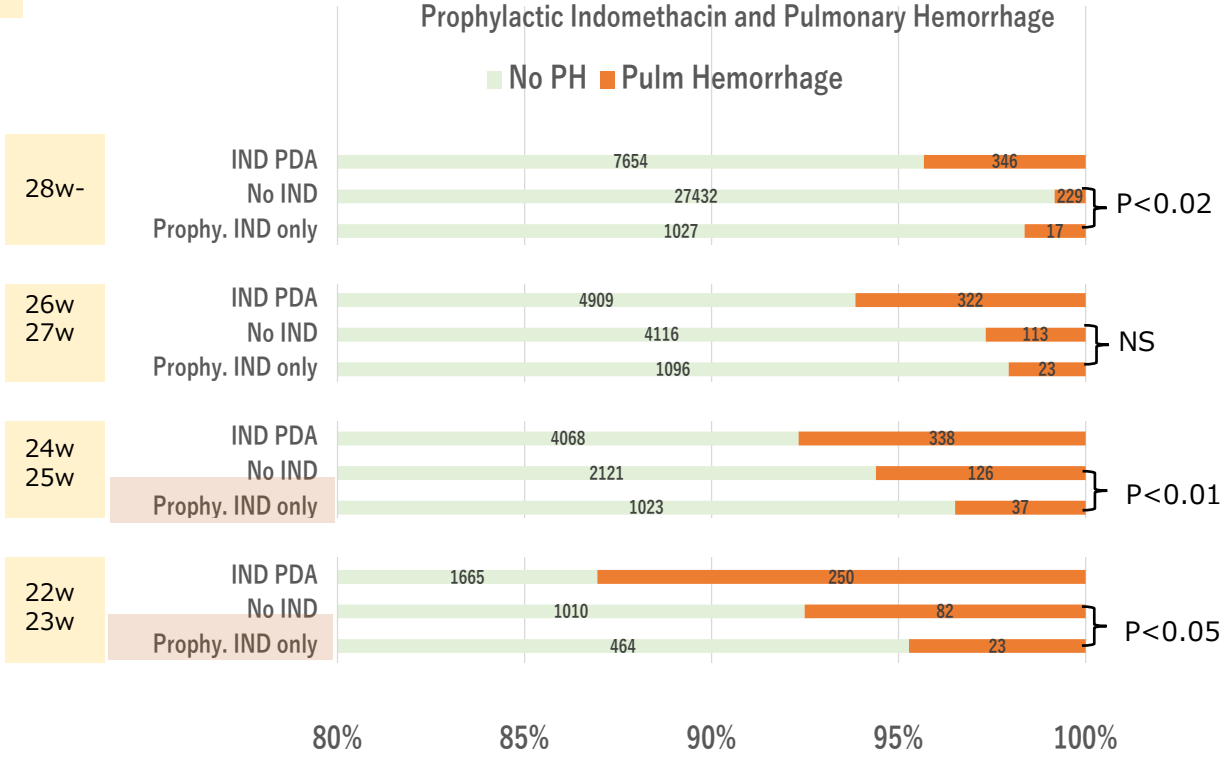
Prophylactic Indomethacin

- In NRNJ-RCT of Prophylactic Indomethacin pulmonary hemorrhage PH was reduced.
- In NRNJ cohort Prophylactic Indomethacin reduced PH compared with no IND in infants <26w.

A randomized placebo controlled trial for the IVH prevention 1998-2003 (NRNJ)
Prophylactic Indomethacin and
Pulmonary Hemorrhage(<1000g)



NRNJ cohort



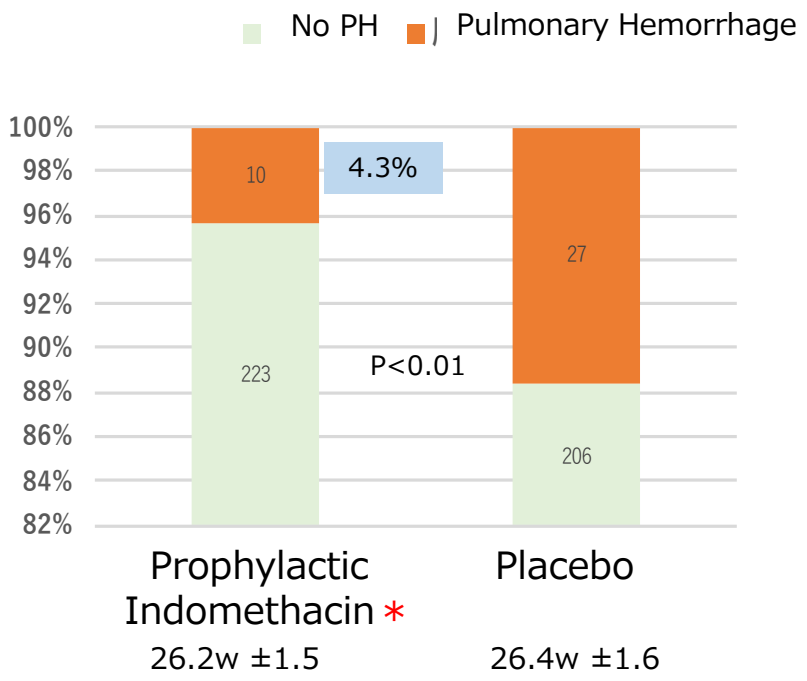
＊ Starting within 6 hours of birth, 3 doses of IND or placebo were given with 6 hours' continuous i.v. infusion every 24 hours. IND was given at the dose of 0.1 mg/kg-wt/dose.

A part of「IND PDA」includes those who were given prophylactic IND together with Indomethacin for their PDA treatment.

Prophylactic Indomethacin

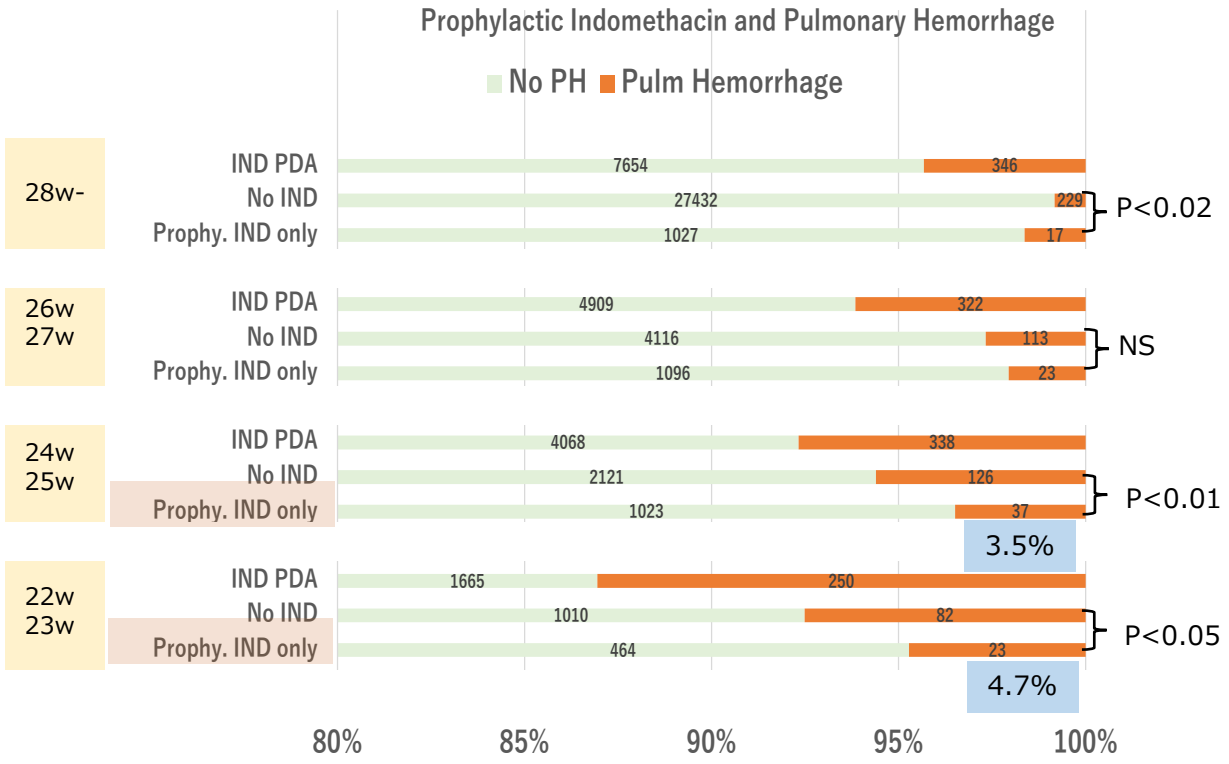
◆ It may be worth to note that the pulmonary hemorrhage ratios of infants given prophylactic IND were very close in RCT 4.3%(10/233), in NRNJ cohort 4.7%(23/487) for 22-23w & 3.5%(37/1060) for 24-25w.

A randomized placebo controlled trial (NRNJ)
Prophylactic Indomethacin and
Pulmonary Hemorrhage(<1000g) 1998-2003



＊ Starting within 6 hours of birth, 3 doses of IND or placebo were given with 6 hours continuous i.v. infusion every 24 hours. IND was given at the dose of 0.1 mg/kg-wt/dose.

NRNJ cohort



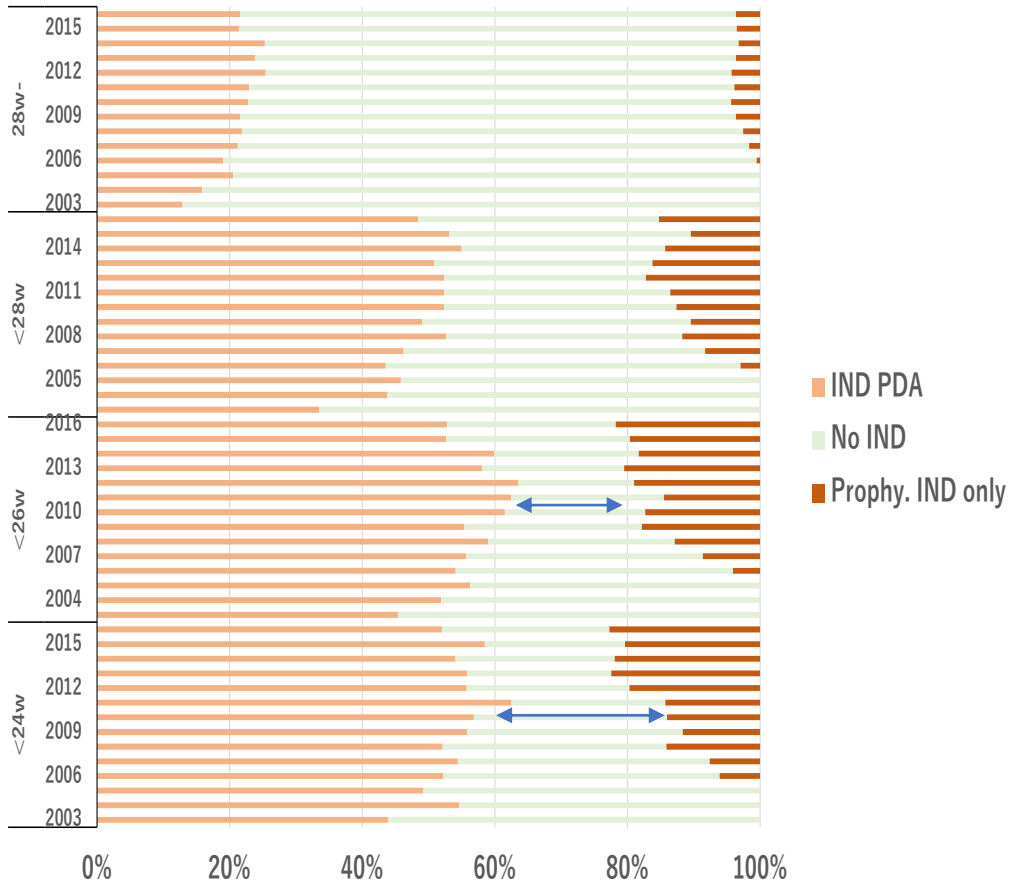
A part of「IND PDA」includes those who were given prophylactic IND together with Indomethacin for their PDA treatment.

There is a room for prophylactic indomethacin.

- Pulmonary hemorrhage is one of three major factors to cause “CP or death at 3 years” in NRNJ database.
- Prophylactic indomethacin can play a significant role in reducing pulmonary hemorrhage.
- The prevalence of P-IND has been around 20% since 2012, and there is a room for P-IND to expand for infants <26w. (Quality Improvement)

NRNJ was involved in the IND clinical trial since 1998.
Intravenous indomethacin was labeled in 2006 in Japan.

	<24w			<26w	
	Prophy. IND only	%P-IND		Prophy. IND only	%P-IND
2006	14	6.1%	2006	20	4.1%
2007	18	7.6%	2007	50	8.6%
2008	33	14.1%	2008	81	12.9%
2009	33	11.7%	2009	104	17.8%
2010	39	14.0%	2010	112	17.3%
2011	48	14.3%	2011	95	14.5%
2012	65	19.7%	2012	138	19.0%
2013	61	22.4%	2013	130	20.5%
2014	62	21.9%	2014	110	18.3%
2015	54	20.4%	2015	112	19.6%
2016	62	22.7%	2016	108	21.8%



Intraventricular Hemorrhage

◆ IVH <1500g total no annual change
24, 25w decreased (<0.01)
22, 23w slowly increased (NS)

◆ Ratio of IVH grade 3 and 4 decreased

<1500g Total

Dependent var. IVH	odds	95% CI	P
Year	1.00	1.00 - 1.01	0.1870

Logistic regression
adjusted with gestational week

28w-

26w
27w

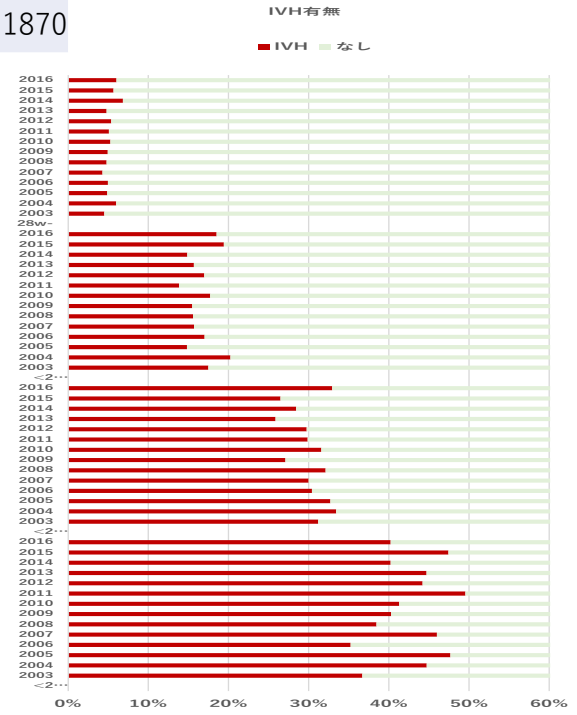
IVH	odds	95% CI	P
Year	0.98	0.96 - 1.00	<0.01

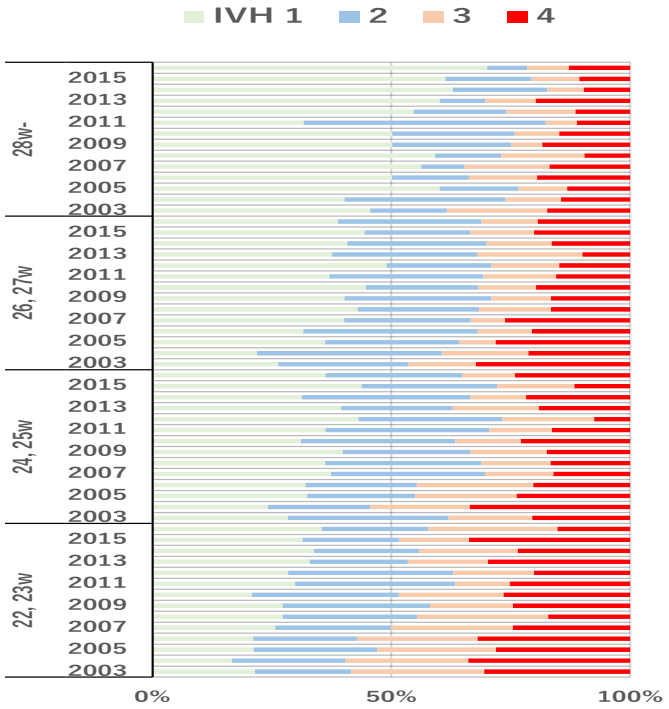
24w
25w

IVH	odds	95% CI	P
Year	1.01	0.98 - 1.04	NS

22w
23w

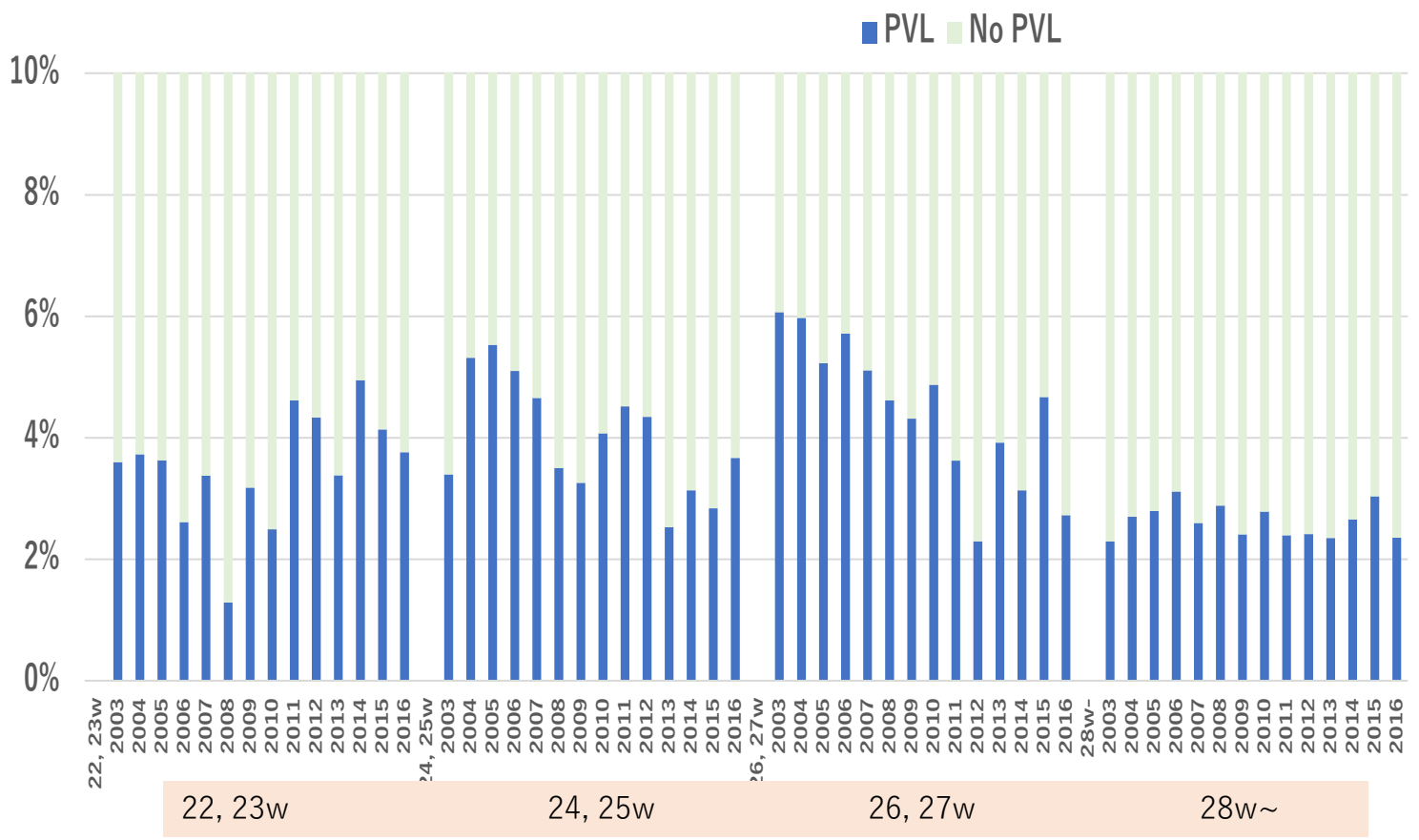
IVH34	odds	95% CI	P
Year	0.97	0.96 - 0.98	<0.001





Periventricular Leukomalacia

◆ PVL significantly decreased in infants of 24, 25w, 26w and 27w.

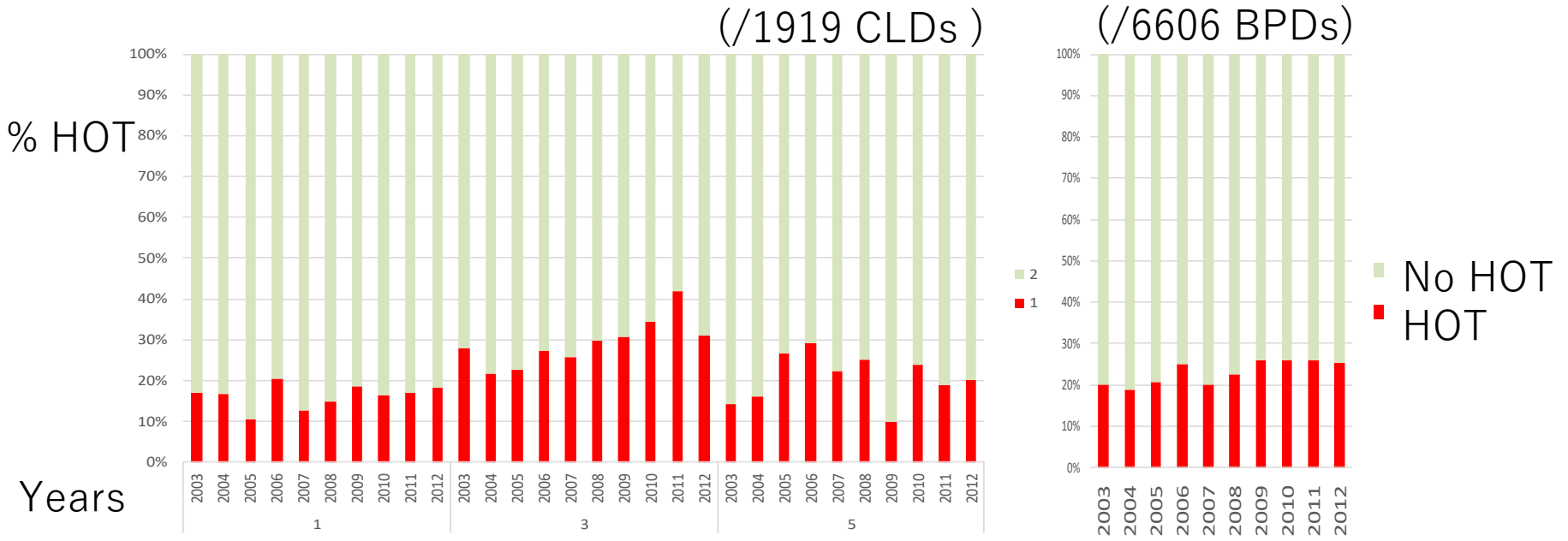


Dependent variable PVL	odds ratio	95%CI	P
22, 23w			
Gestation	0.97	0.65 -1.43	0.86
Year	1.03	0.98 -1.08	0.20
24, 25W			
Gestation	0.9	0.89 -0.91	<0.001
Year	0.98	0.97 -0.99	0.002
26, 27w			
Gestation	0.9	0.89 -0.91	<0.001
Year	0.98	0.97 -0.99	0.002
28w~			
Gestation	0.76	0.73 -0.79	<0.001
Year	1	0.98 -1.01	0.73

Logistic regression

Home Oxygen therapy
(CLD type 1, 3, 4 & BPD36w)

◆ HOT was increasing in CLD type 3 and BPD36w.



CLD type 1	type 3	type 4	BPD36w
HOT	HOT	HOT	HOT
Year odds 1.03	Year odds 1.08	Year Odds 1.02	Year odds 1.05
95%CI 0.99-1.07	95%CI 1.04-1.12	95%CI 0.92-1.13	95%CI 1.02-1.07
P NS	P <0.0001	P NS	P <0.0001

Logistic regression, adjusted for gestation

Definition

Classification of Chronic Lung Disease *

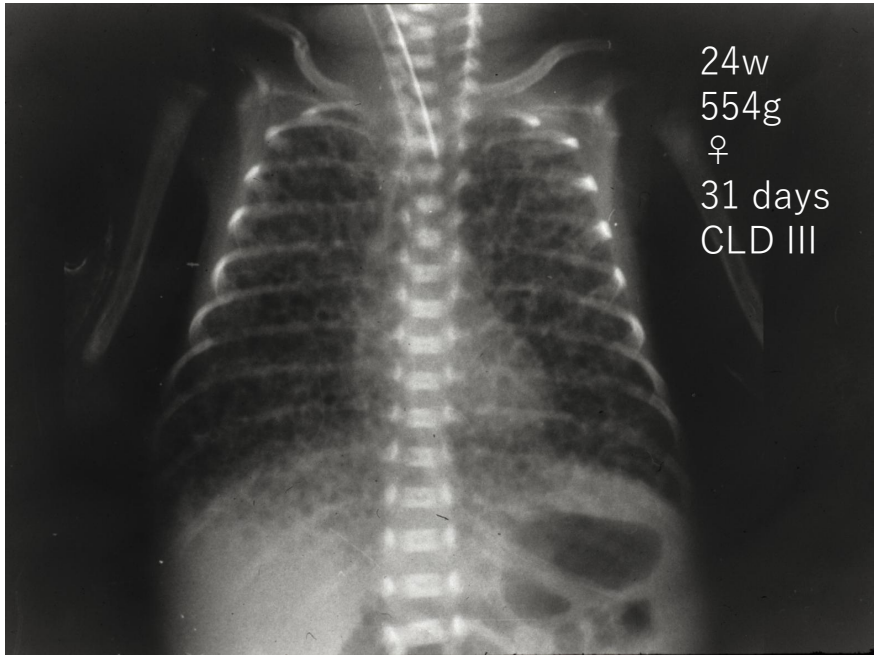
＊Oxygen therapy >28days of age

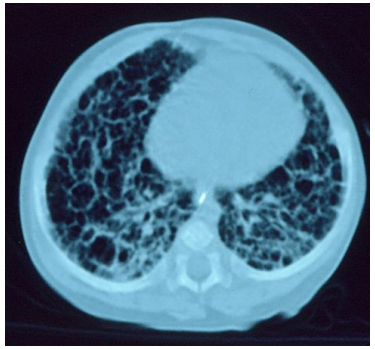
Type of CLD	RDS	High serum IgM、Chorioamnionitis, Funicitis	Bubbly/cystic Chest X-ray >28days
Ⅰ	＋	—	＋
Ⅱ	＋	—	—
Ⅲ	—	＋	＋
Ⅳ	—	Unknown	＋
Ⅲ’	—	＋	—
Ⅴ	—	—	—
Ⅵ			

CLD Group, MCH Grant（Yunosuke Ogawa 1992、Masanori Fujimura 1996).

Ogawa Y, Fujimura M et al. Epidemiology of Neonatal Chronic Lung Disease in Japan. Acta Paediatr Jpn 1992;34:663-667

CLD type III;
Bubbly/cystic appearance on chest X-ray





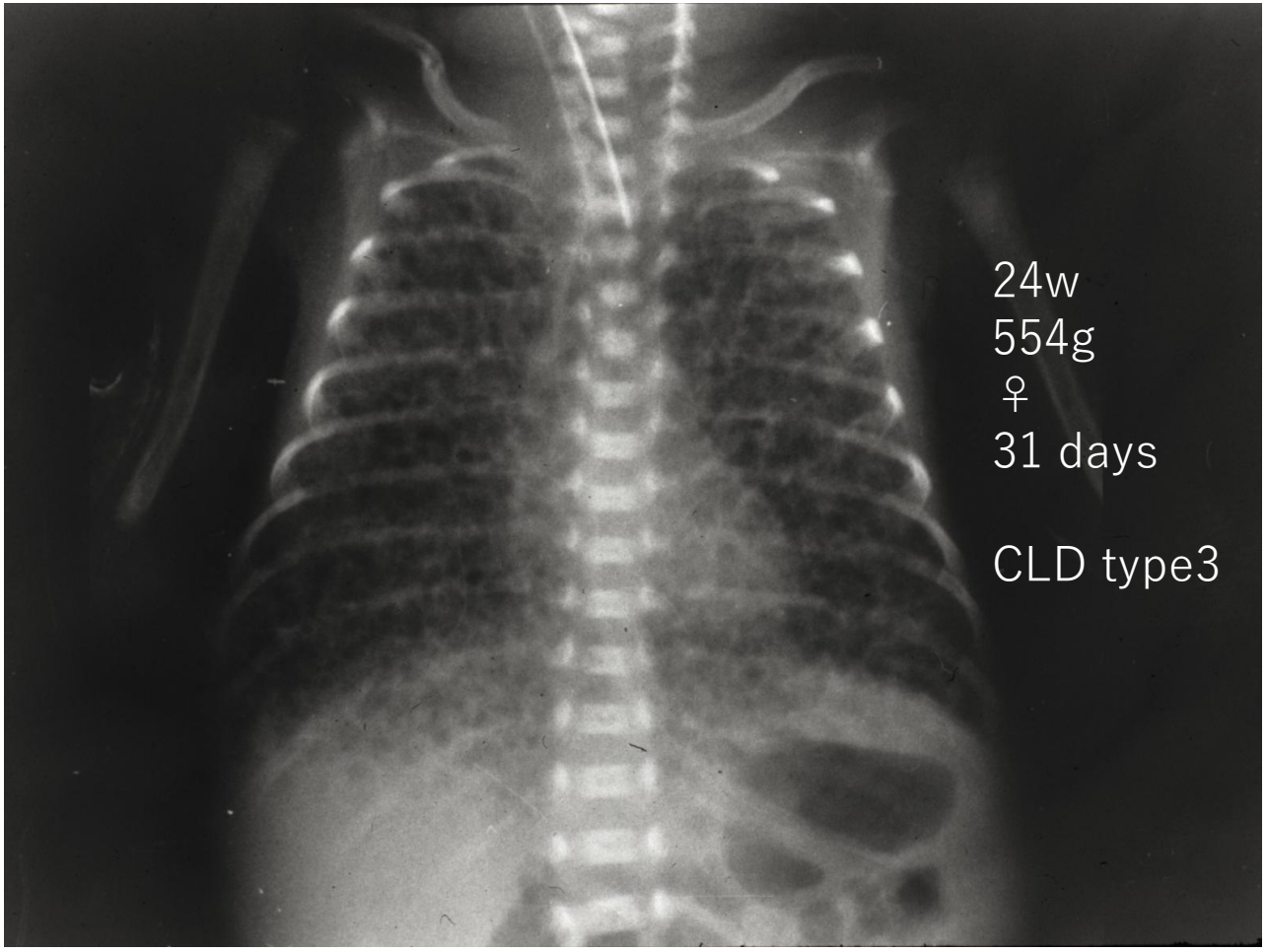
Emphysema of CLD Type Ⅲ

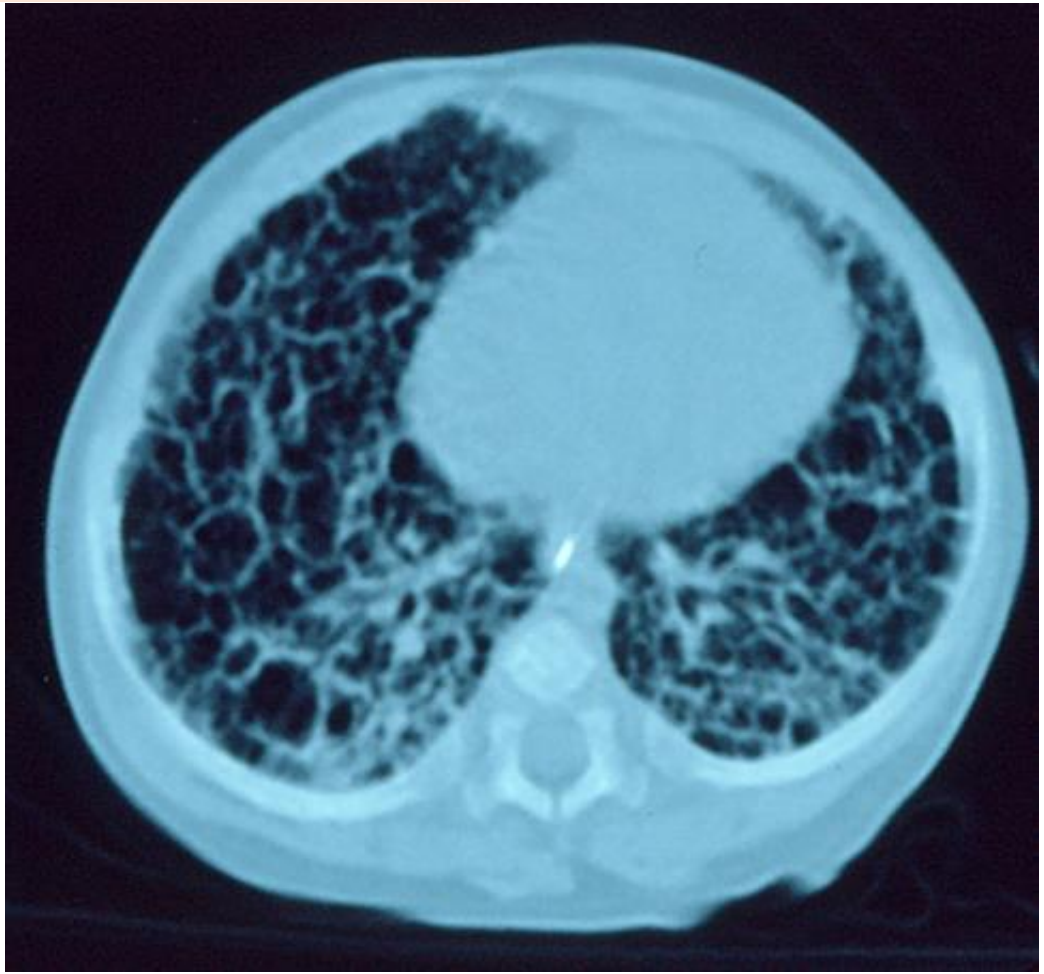
Cystic/bubbly appearance

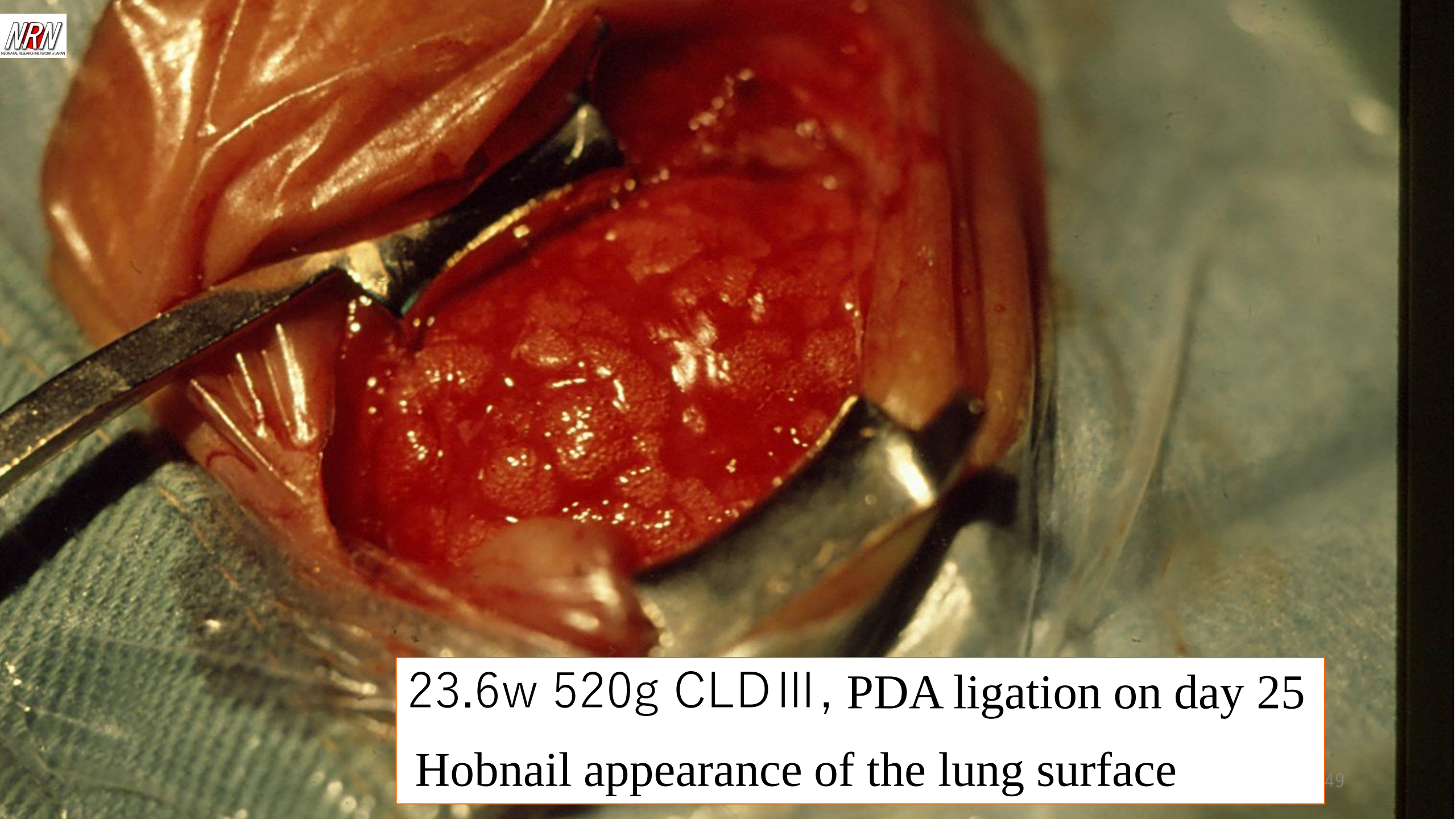
① diffuse

② Foamy cystic

③ Not interstitial





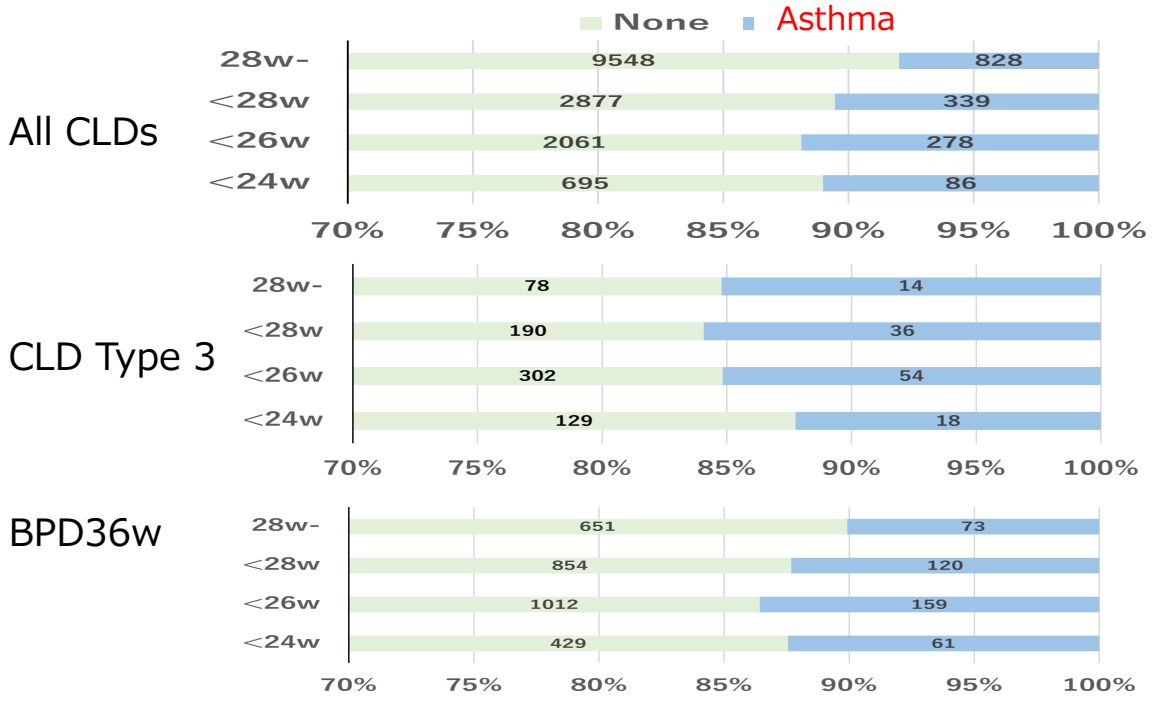


23.6w 520g CLDⅢ, PDA ligation on day 25

Hobnail appearance of the lung surface

Chronic Lung Disease & Bronchial Asthma (3 years)

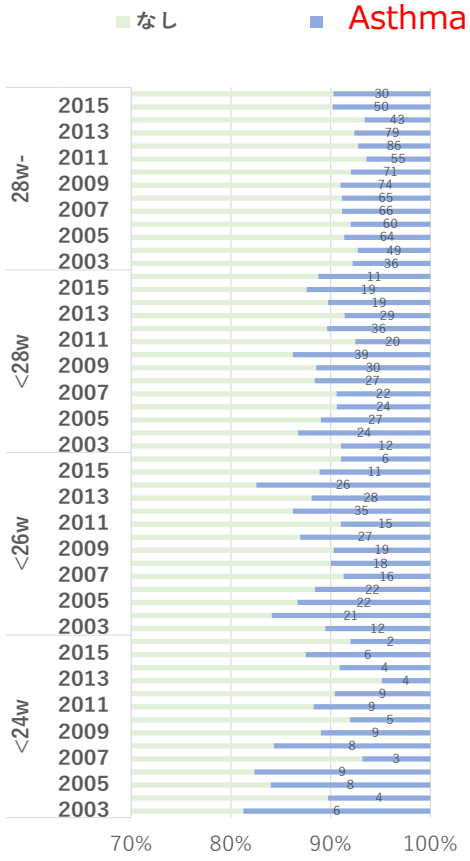
◆ Bronchial Asthma (3 years) significantly correlated with CLD Type 3, but not with BPD36w



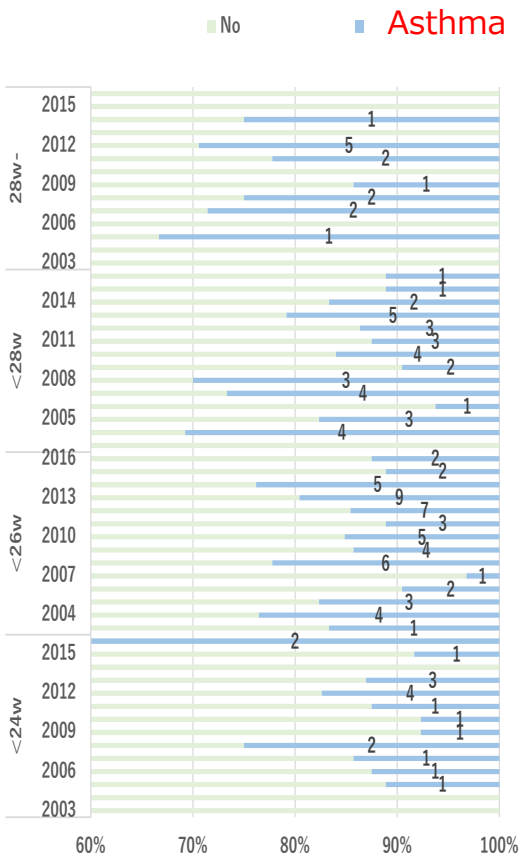
Dependent var. Asthma	odds	95%CI	P
CLD Type 3	1.36	1.10 - 1.69	0.005
BPD36w	1.16	0.99 - 1.37	0.068
Gestational week	0.99	0.96 - 1.03	NS
Year	1.00	0.98 - 1.02	NS

Logistic regression

All CLDs



CLD Type 3



Summary
-Neonatal Factors-

1. 1 min & 5 min Apgar Scores declined after Level 2 & 3 NICUs merged in 2010.
2. RDS increased and pulmonary hemorrhage decreased. Air leak showed no significant change. PPHN increased.
3. The main reason of increasing RDS may be correlated with increase of Cesarean section.
4. Why pulmonary hemorrhage decreased with RDS increasing? The answer will be increasing administration of prophylactic indomethacin.
5. IVH slowly increased for 22, 23w(NS) and decreased for 24, 25w(<0.01). IVH grade reduced.
6. PVL significantly decreased in categories 24, 25w and 26, 27w.
7. Hot was increasing in CLD type 3 and BPD36w.
8. Bronchial Asthma (3 years) significantly correlated with CLD type 3, but not with BPD36w.

Limitations and advantages of NRNJ database

Limitations

1. A large proportion of infants “Not Available” has been a major limitation in NRNJ database.
2. NRNJ depends much of work for data collection upon NRNJ colleagues.

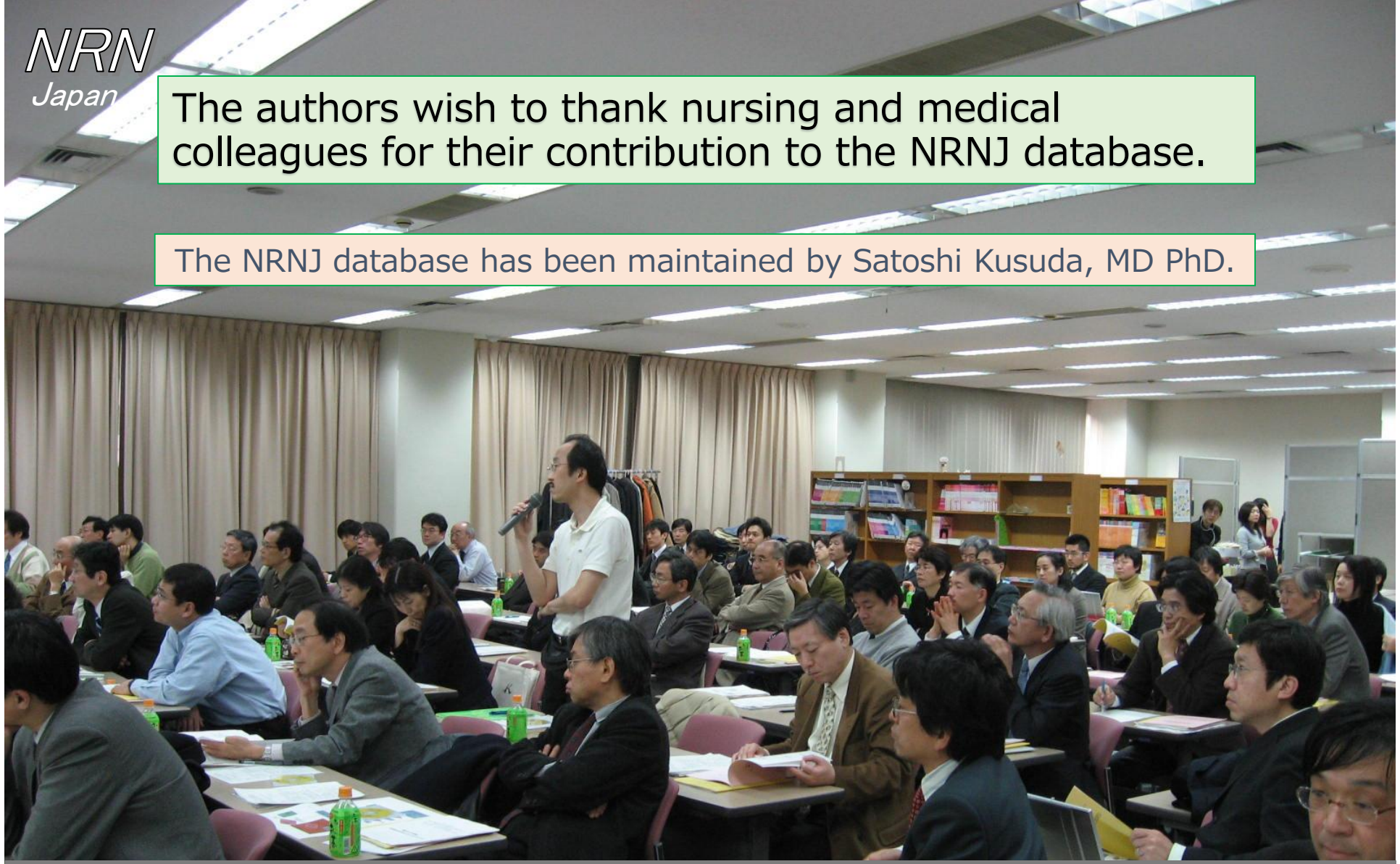
Advantages

1. NRNJ database is comprised of very low birthweight infants cared in level 3 and 2 neonatal units and cover 65% census of Japan. “universal”
2. NRNJ is a non-profit organization with a continued support from neonatal professions. “independent and sustainable”
3. NRNJ database is the real world data, and it has been shown to produce the real world evidence. On NRNJ database more than 50 articles were published by NRNJ colleagues in peer reviewed journals.
4. The neonatal network database has the potential to excavate a wide range of neonatal evidences with quick and efficient manner.

NRN
Japan

The authors wish to thank nursing and medical colleagues for their contribution to the NRNJ database.

The NRNJ database has been maintained by Satoshi Kusuda, MD PhD.



Masanori Fujimura	Osaka Women's & Children's Hospital
Satoshi Kusuda	Kyorin Medical University
Yumi Kono	Jichi Medical University
Hidehiko Nakanishi	Kitasato University Medical School
Shinya Hirano	Osaka Women's & Children's Hospital
Naohiro Yonemoto	Department of Public Health, Juntendo University

Neonatal Research Network of Japan

Ministry of Health, Labor and Welfare, Japan

Year	Research Grant in Yen	(US $)
2004	¥30,000,000	$272,727
2005	¥31,320,000	$284,727
2006	¥30,000,000	$272,727
2007	¥34,000,000	$309,091
2008	¥28,012,000	$254,655
2009	¥33,000,000	$300,000
2010	¥21,632,000	$196,655
2011	¥25,958,000	$235,982
2012	¥25,958,000	$235,982
Total	¥259,880,000	$2,362,545

Financial supporter 2013~;
Japan Society for Neonatal Health and Development and others