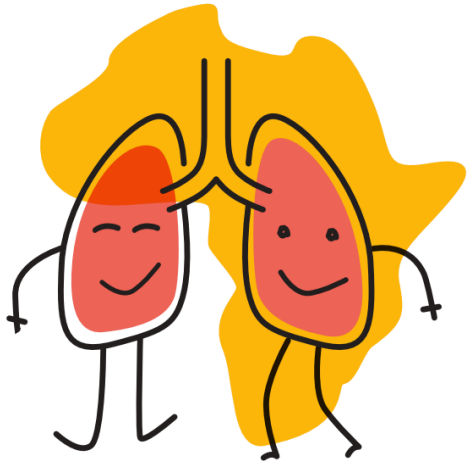
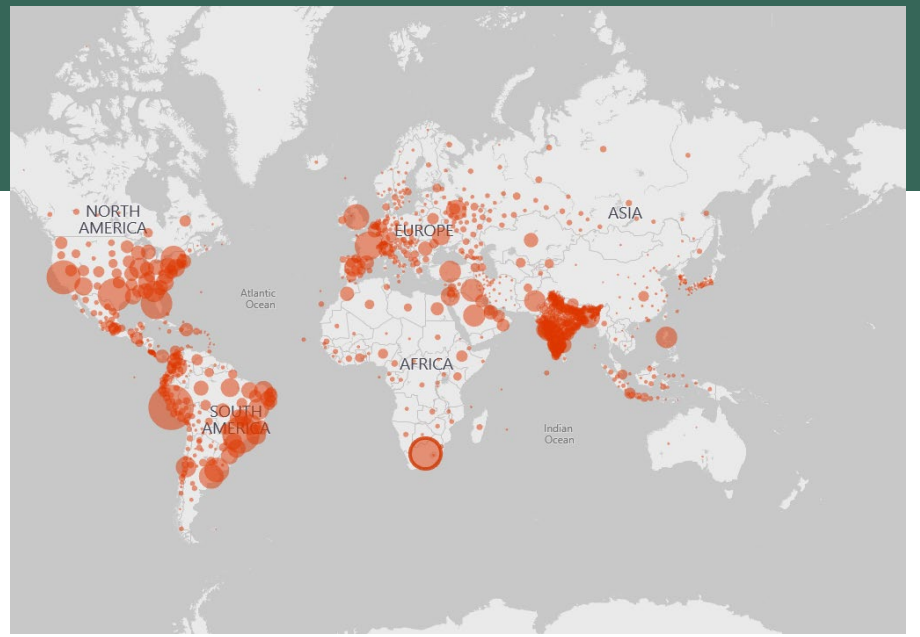
LUNG FUNCTION IN THE TIME OF COVID-19

AFRIPAEDLF WORKING GROUP MEETING, 1 OCTOBER 2020

DI GRAY



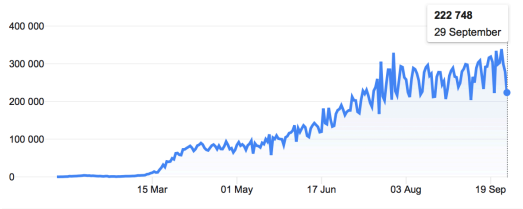
LUNG FUNCTION AND COVID-19 RISK



Worldwide

Total cases

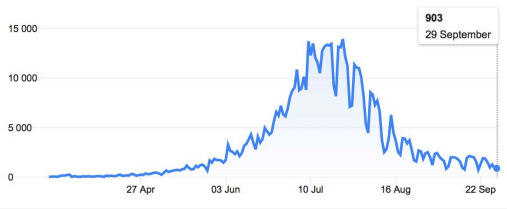
33,7M



South Africa

Total cases

673K



- Key concern around lung function and infectious risk
  - Aerosolising, especially forced manoeuvres
  - Exposing at risk patients to infectious spaces

CHILDREN AND INFANTS

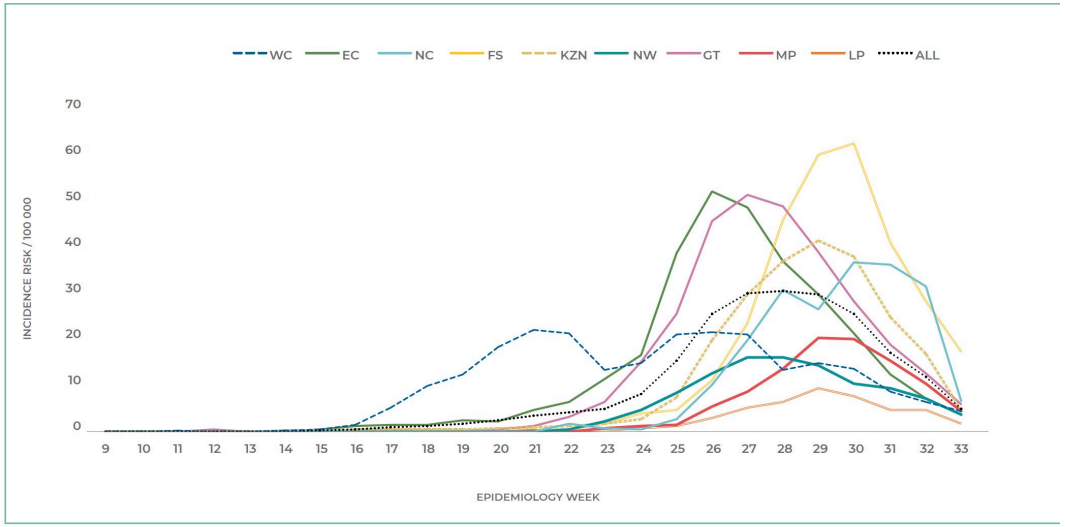


Figure 1. Weekly incidence risk of laboratory-confirmed COVID-19 among children and adolescents ≤18 years by province by epidemiologic week, South Africa, 1 March- 17 August 2020 (N=44 956).

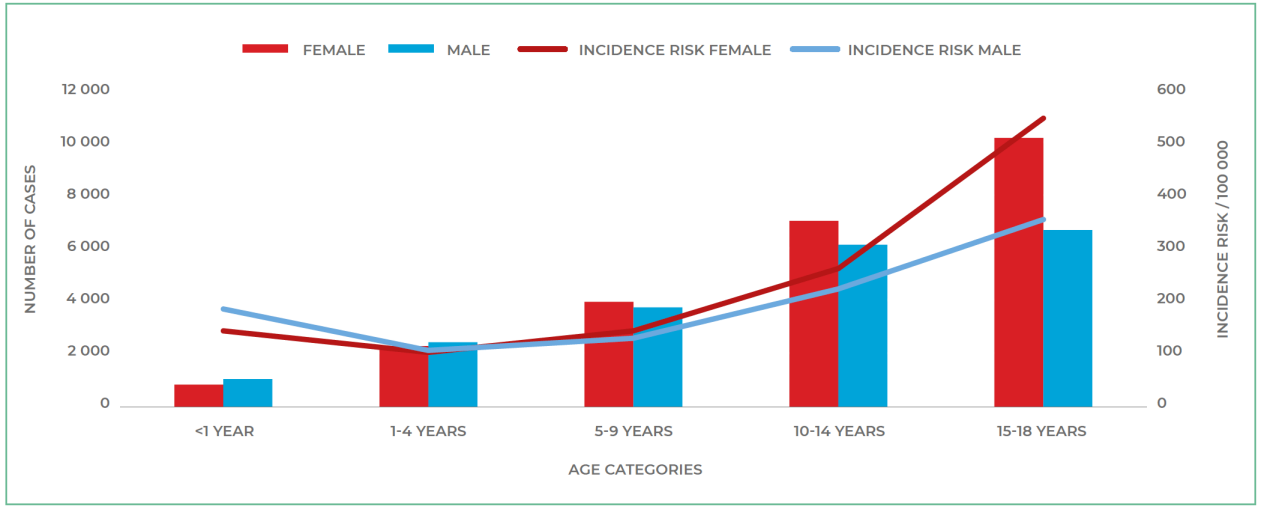


Figure 2. Cumulative incidence risk of laboratory-confirmed COVID-19 among children and adolescents by age and gender, South Africa, 1 March-17 August 2020 (N=44 956).

- South Africa: children 7.6% of laboratory confirmed cases and 2.9% of admissions;

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SOUTH AFRICAN THORACIC SOCIETY
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22 Ap

POSITION STATEMENT OF THE SOUTH AFRICAN THORACIC SOCIETY (SATS) O CONDUCT OF LUNG FUNCTION TESTING DURING THE CORONA VIRUS COVI PANDEMIC

SATS acknowledges the seriousness of the corona virus COVID-19 pandemic. It suppo National Department of Health in its efforts to contain the pandemic and minimise spread.

SATS, in line with international respiratory society guidelines, recommends that no lung tests must be conducted during this period. This includes the performance of peak flow te hospitalised patients admitted with acute asthma. This recommendation is based on the obviate or minimise aerosolization procedures that may contribute to the spread of the virus.

In the event there is an absolute need for the conduct of any lung function test, it requested and conducted under strict supervision, preferably by a pulmonologist. The pr must be conducted with optimal infection control and use of full personal protection equ (PPE) as per national guidelines.

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30 September 2020

UPDATE: POSITION STATEMENT OF THE SOUTH AFRICAN THORACIC SOCIETY (SATS) ON PULMONARY FUNCTION TESTING (PFT)

The South African Thoracic Society, in line with other international respiratory societies, recommends that pulmonary function testing can be reintroduced where there is a clinical or other substantial indication for testing, provided personnel and subjects are adequately protected from contracting SARS-CoV-2. While it remains the employer's responsibility to provide pulmonary function technologists and other individuals involved with a safe working environment, SATS recommends the following:

1. There should be an important clinical or other substantial indication (including compensation and research) to perform testing. Deferring testing should be considered where the perceived risk outweighs the benefit.
2. Personnel performing the test should be assessed for risk of severe COVID-19 disease, and high-risk personnel should not be forced to perform PFTs.
3. Individuals undergoing lung functions should be screened, and risk for COVID-19 assessed by questionnaire (see updated case definition at https://www.nicd.ac.za/wp-content/uploads/2020/07/NICD_DoH-COVID-19-Guidelines_Final_3-Jul-2020.pdf)
4. PFTs may be performed 4 weeks after symptom onset in individuals who had proven or highly likely symptomatic COVID-19, and a negative screen (as per point 3).
5. Testing capacity/volumes should at the present time preferably be escalated to no more than 50% of pre-COVID capacity, to allow for adequate time between subjects to ensure safety in addition to measures to ensure social distancing.
6. The contact time between personnel and subjects should be minimised, wherever possible.

Recommendation from ERS Group 9.1 (Respiratory function technologists /Scientists)

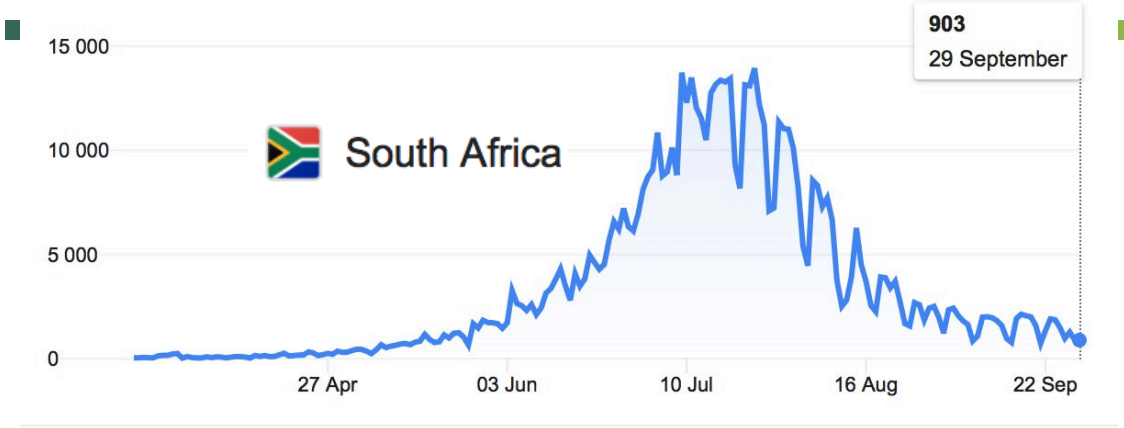
Lung function testing during COVID-19 pandemic and beyond

We recommend the following safety measures for lung function testing based on the prevalence of COVID-19 in the community:

Pandemic phase	**High community prevalence**	**Level 1 safety recommendations**
Post Peak phase	**Low community prevalence**	**Level 2 safety recommendations**
Post Pandemic phase	**Controlled**	**Level 3 safety recommendations**

Recommendations for Pandemic Phase - Level 1 safety

During high prevalence of the virus in the community, referring personnel must carefully consider the safety of staff, cross-contamination of equipment and therefore restrict referrals to patients requiring urgent / essential tests only for immediate diagnostics of current illness.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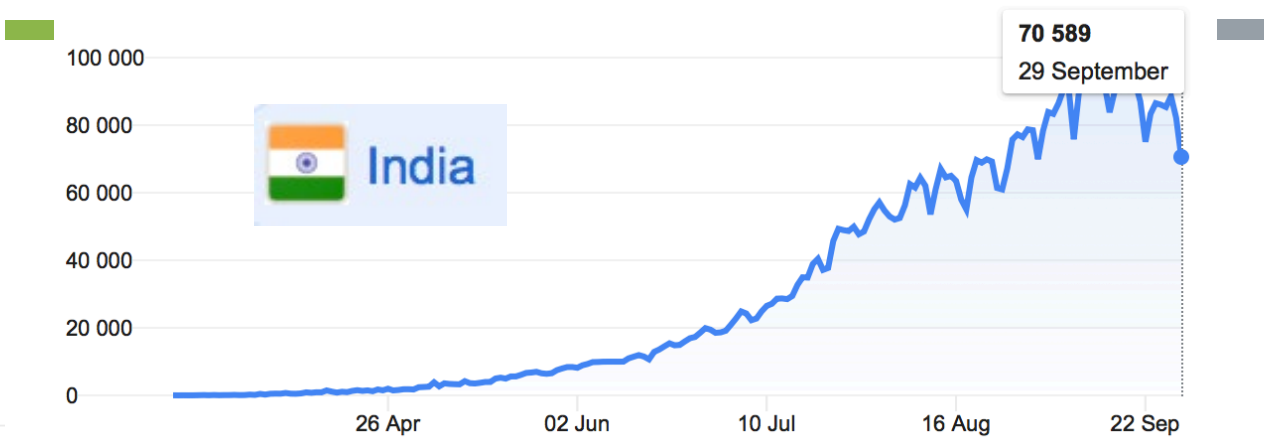
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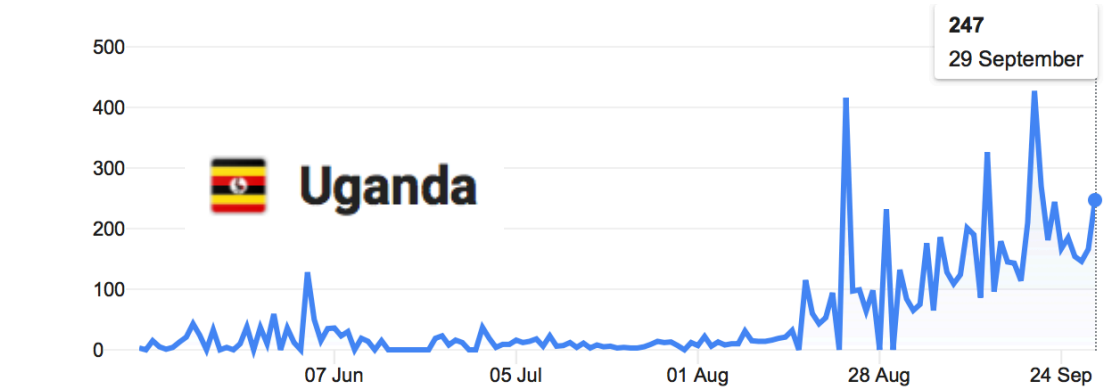
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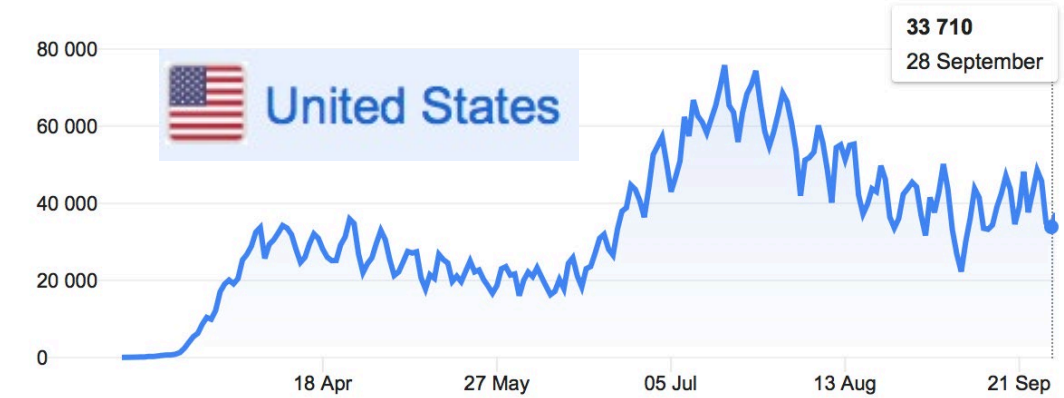
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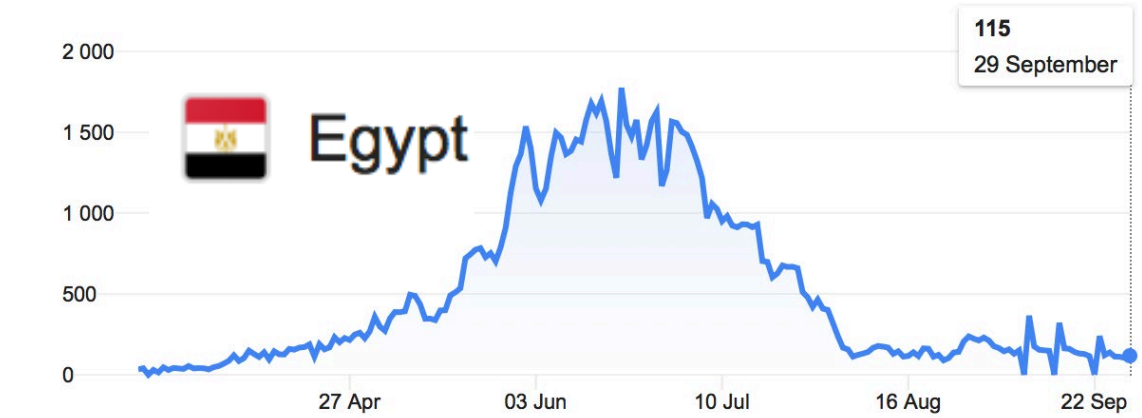
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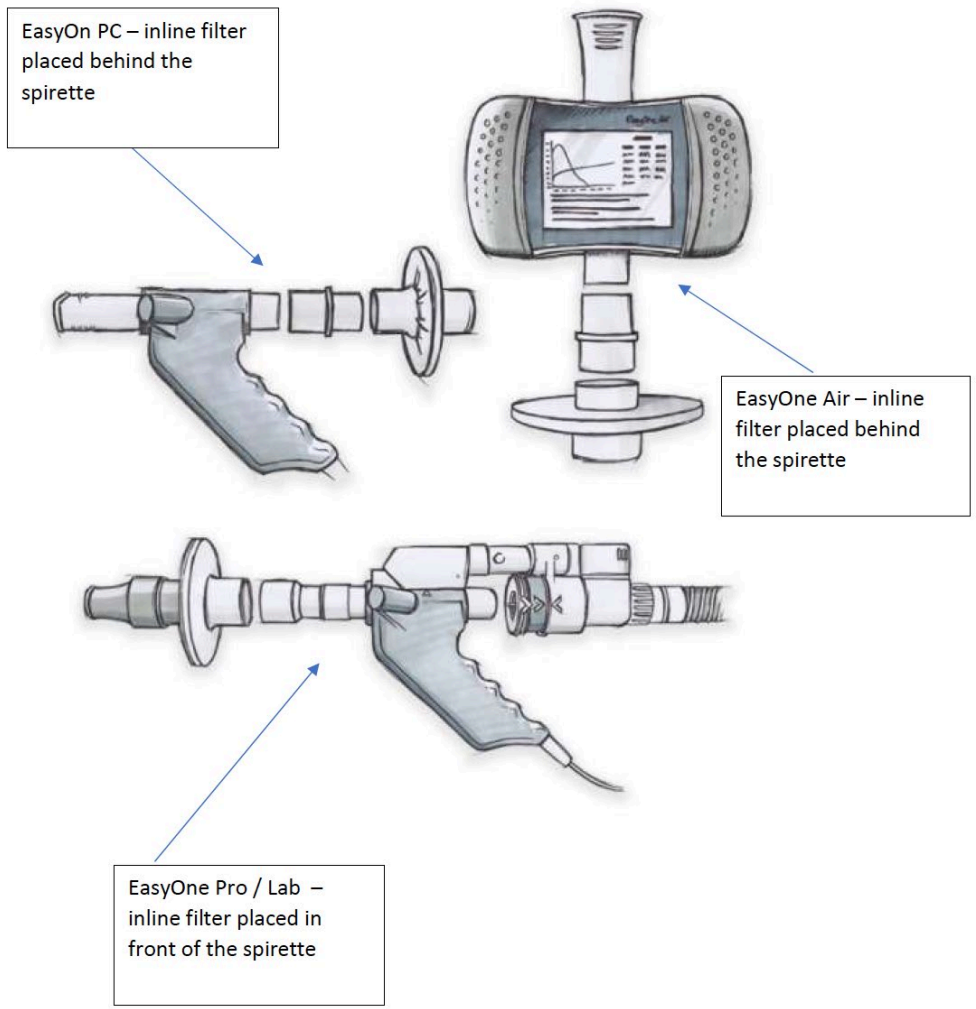
BASIC PRINCIPLES – OUR APPROACH

Spirometry (and other Lung Function) Testing during COVID-19 PROTOCOL

- **Key Messages:**
- Only tests that will inform key diagnostic or management decisions should be done
- No one acutely sick or within 2 weeks of COVID exposure should be tested
- Careful attention to **strict infection control** and PPE; book less patients, space them to avoid clustering and allow time between tests.
- Tidal breathing measures (oscillometry, FeNO, MBW) are less aerosolising than spirometry and are safer. Consider using where appropriate to your clinical question
- Avoid bronchial provocation and exercise testing

Strict infection control

- Screening: at booking and arrival
- Avoid crowding: booking, spacing in waiting room, reduce people in lung function room
- Good ventilation: negative pressure or open windows
- Masks and visors
- Strict hand hygiene
- Equipment and used surfaces: wiped down between testing
- Filters: single use (cf. NDD ultrasonic flow meters need additional filter)
- After test clean and leave room for 15 min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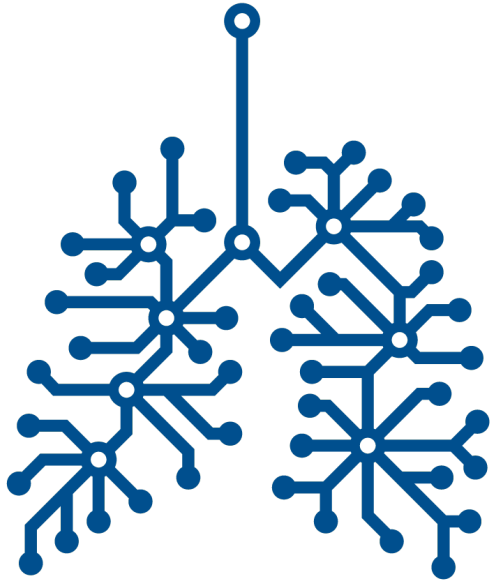
EasyOne Air – inline filter placed behind the spirette
EasyOne Pro / Lab – inline filter placed in front of the spirette

DISCUSSION

ERS



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ERS 2020: Paediatric Respiratory Physiology Summary

Kathryn Ramsey

University Children's Hospital Bern, Switzerland

Paediatric Respiratory Physiology sessions

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Oral sessions:

- Chronic respiratory diseases and their origins in early life - how physiology meets clinical medicine
- Covid-19 Impact in children with chronic lung conditions
- Live from the clinic (procedure videos) - paediatric procedures and physiology
- New frontiers in CF imaging and lung physiology
- Respiratory physiology and sleep: from neonates to adults

Poster sessions:

- Respiratory physiology and sleep: new approaches to diagnosis and treatment
- Respiratory physiology and sleep: from neonates to adults
- Clinical monitoring and new therapies for cystic fibrosis

Chronic respiratory diseases and their origins in early life: how physiology meets clinical medicine

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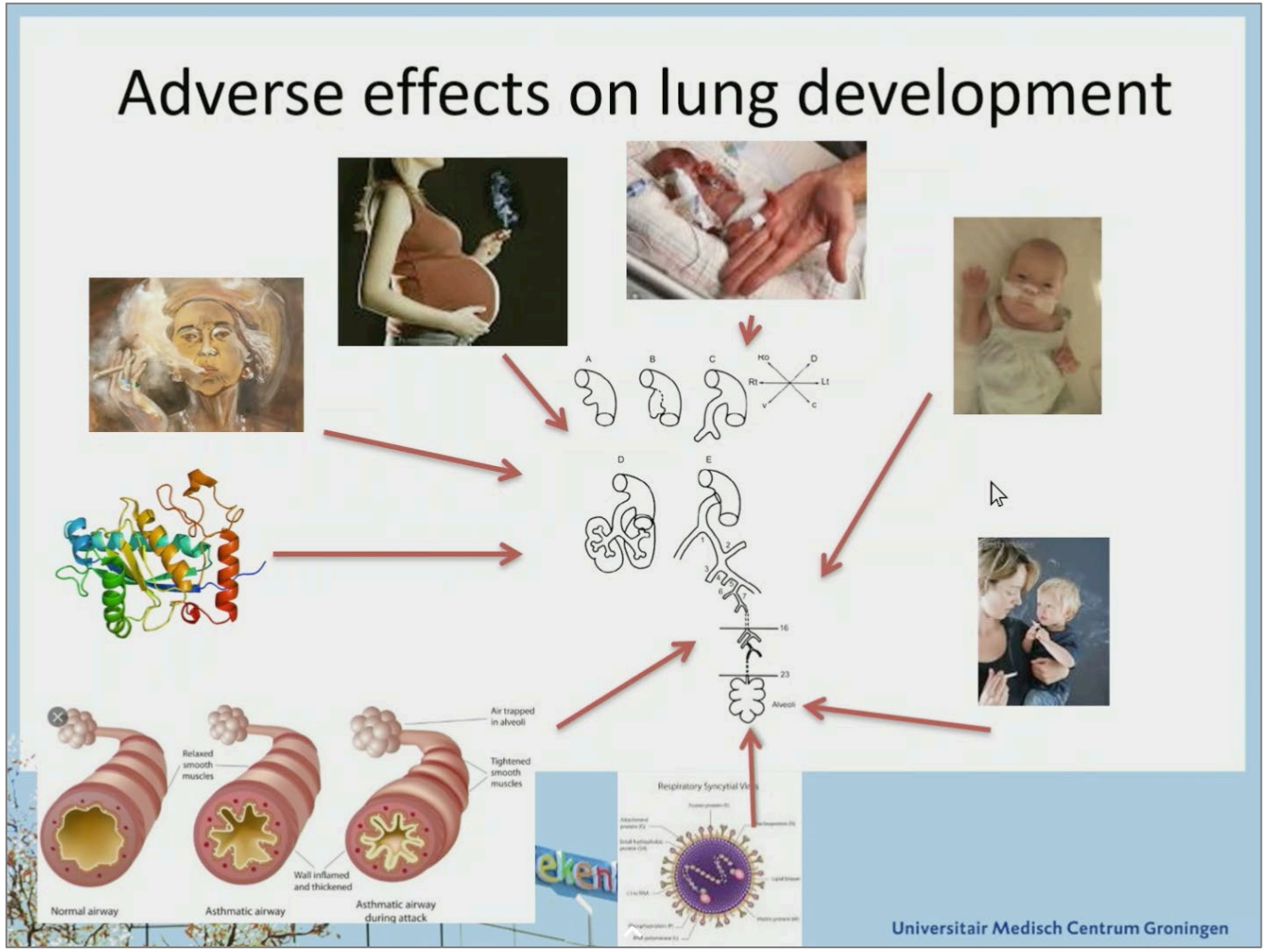
Elianne Vrijlandt (Netherlands)

Summarised impact:

- Transgenerational impacts
- *In utero* smoking
- Premature birth / BPD
- Parental smoking
- Viral infections
- Maternal/paternal asthma
- Gene-environment interactions



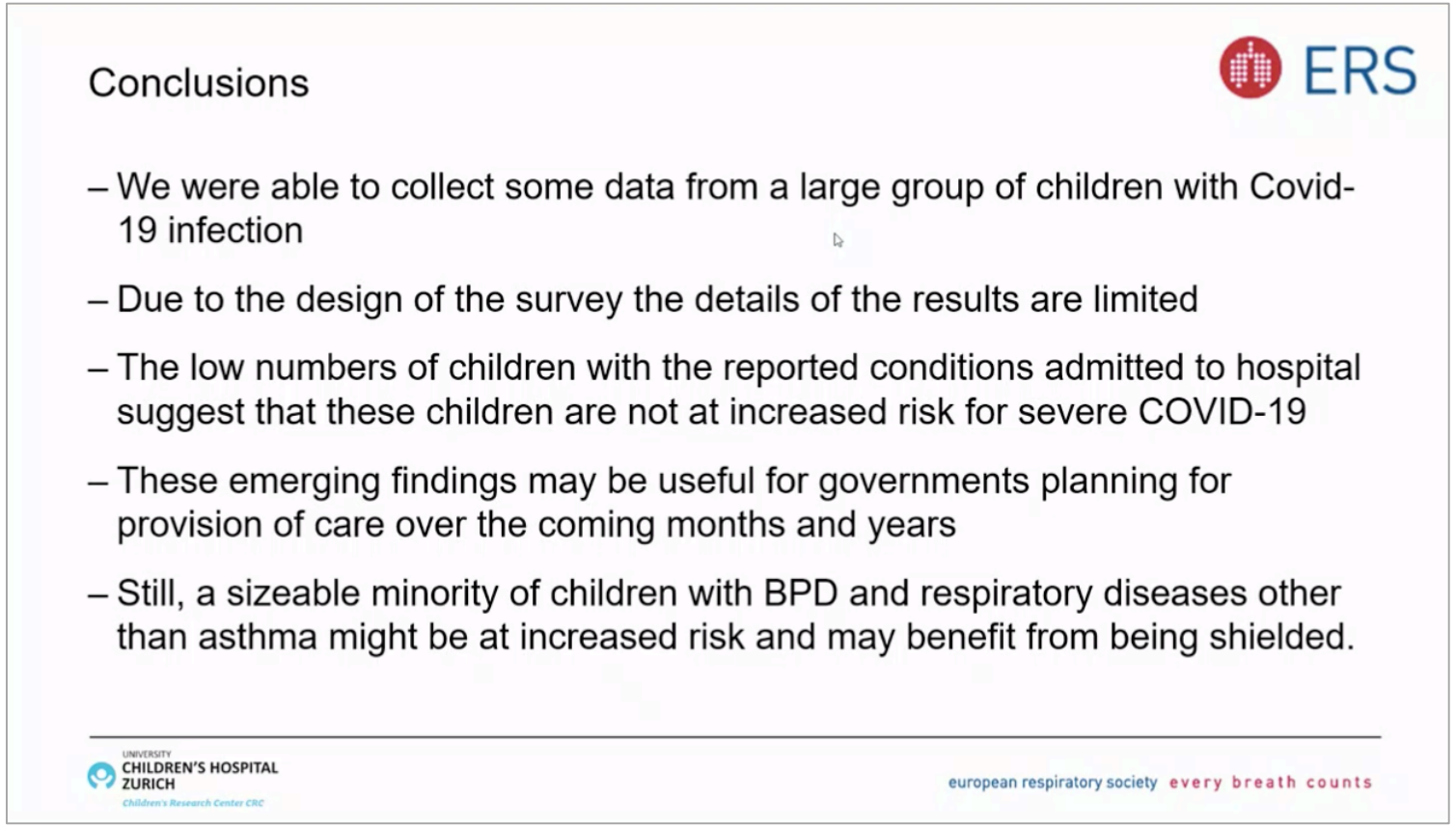
Chronic respiratory diseases and their origins in early life: how physiology meets clinical medicine

Alexander Möller (Zurich)

ERS survey of Covid-19 in children with respiratory conditions including asthma, cystic fibrosis, and BPD

- March 2020
- 174 centres responded
- 94 centres with cases in 945 children

Emerging data suggests children with respiratory conditions not at increased risk for severe Covid-19 infection



New frontiers in CF imaging and lung physiology

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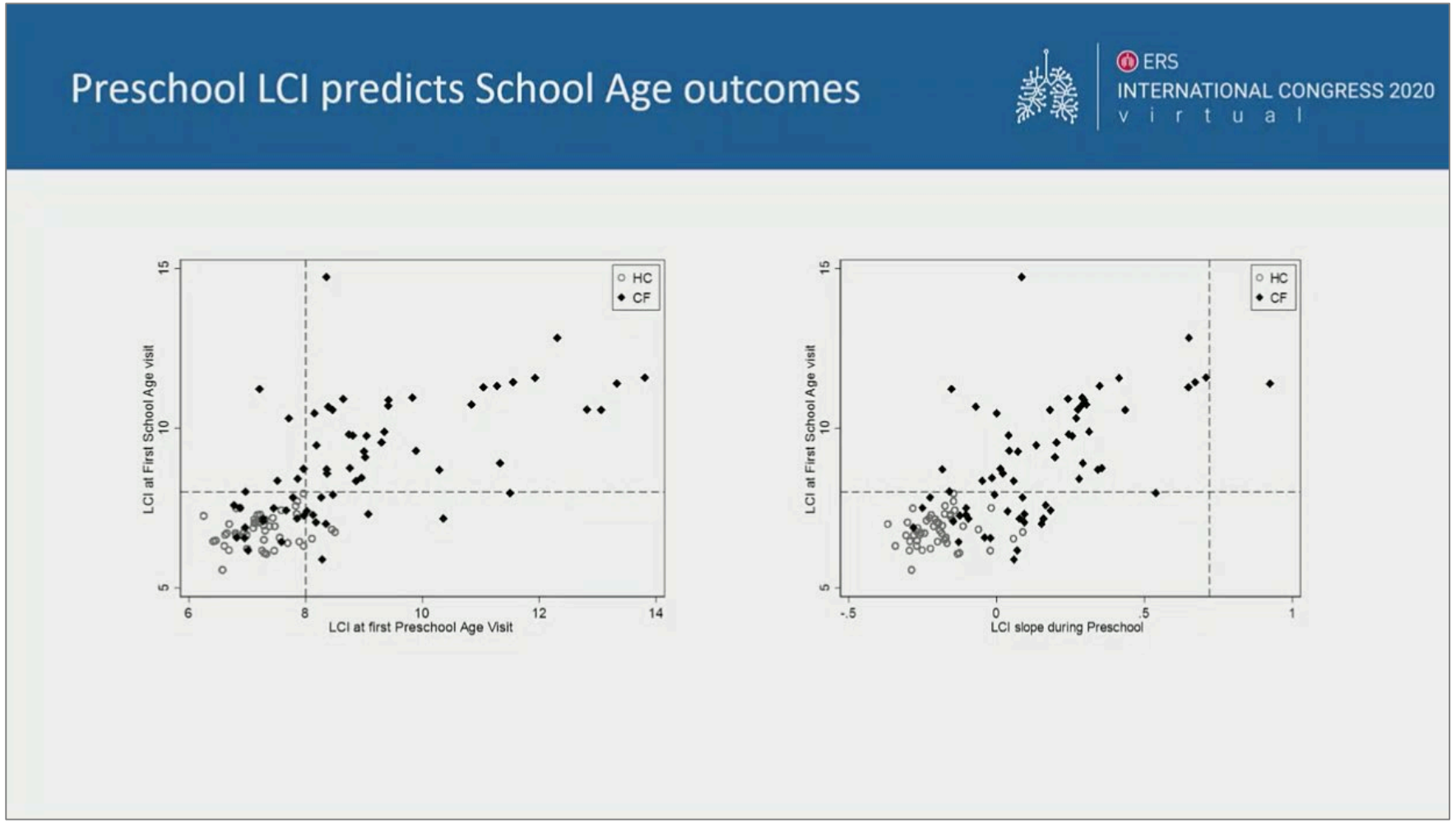
Sanja Stanojevic (Toronto):

- 64 CF children and 50 healthy controls
- Longitudinal 3 monthly MBW outcomes at preschool (3-4y) and school age (5-10y)
- Mean LCI and LCI slope during preschool years associated with LCI at school age
- Higher rate of hospitalisations associated with higher LCI
- LCI relatively stable during school age years



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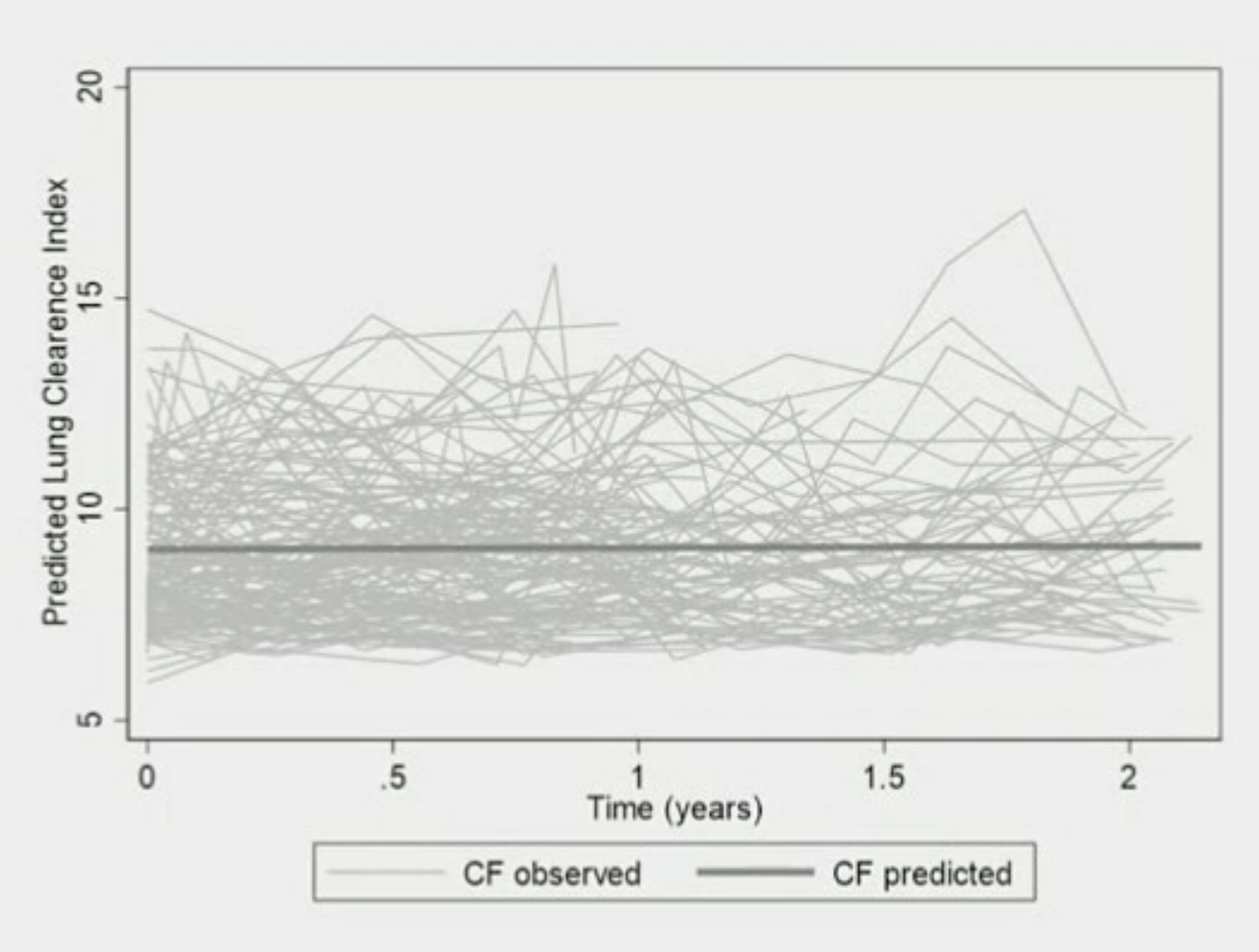

New frontiers in CF imaging and lung physiology

ERS INTERNATIONAL CONGRESS 2020 virtual

Bettina Frauchiger (Bern):

- 71 CF children (907 visits)
- Longitudinal 3 monthly MBW at routine clinical surveillance
- LCI relatively stable in preschool and school-age, increases during adolescence
- Risk factors: aspergillus, pseudomonas, exacerbations, CF related diabetes, ABPA
- Steeper increase in females (mostly explained by higher incidence of risk factors)

Main findings

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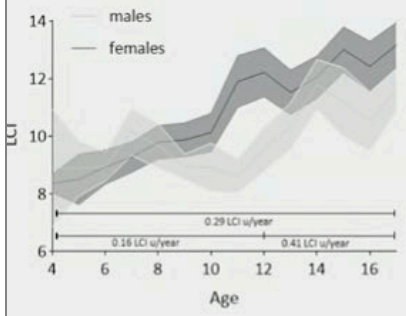
- Study period 2011-2018
- CF subjects attending routine care at the children's university hospital in Bern
- *Inclusion criteria*: Age 3-18 years; acceptable LCI data along with matching clinical data; minimum 3 visits
- 71 subjects, 907 visits with acceptable LCI data

Unadjusted increase in LCI

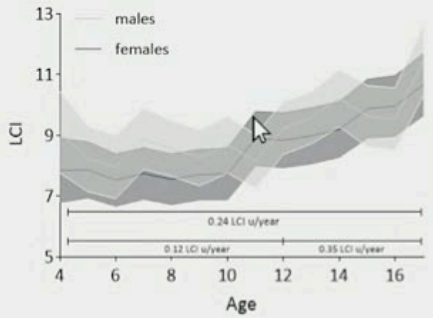


- Increase pronounced in adolescence
- Earlier increase in females

Risk factors associated with an increased LCI

- Aspergillus fumigatus
- Pseudomonas aeruginosa
- Pulmonary exacerbations
- CF-related diabetes
- ABPA (bronchopulmonary aspergillosis)

Increase in LCI when adjusting for risk factors



- LCI increases also in absence of risk factors
- Prevalence of risk factors explained the different patterns in males and females

Respiratory physiology and sleep: from neonates to adults

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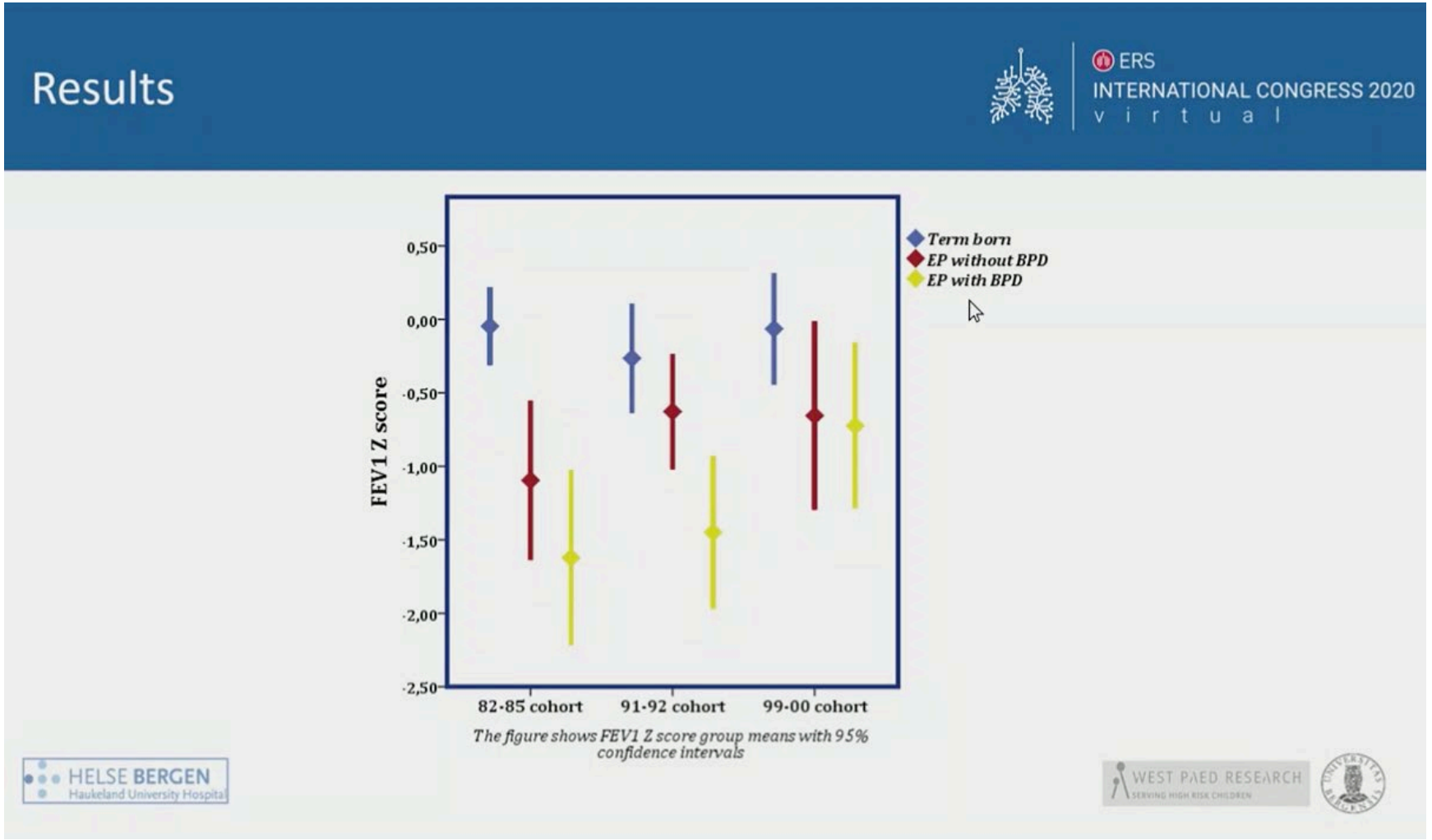
Tonja Bårdsen (Norway):

- Spirometry outcomes in former pre-terms vs term born controls
- Extremely preterm born subjects
  - GA ≦28 wks, BW ≦1000g
  - Born in 3 decades (80s, 90s, 00s)
  - N = 30-50 per group
- Worse FEV_1 in pre-terms but improvement over time, especially in BPD



Respiratory physiology and sleep: from neonates to adults

ERS INTERNATIONAL CONGRESS 2020 virtual

Yasmin Salem (Bern):

- Impact of caesarean section on respiratory outcomes in first year of life
- 580 healthy infants with weekly surveillance (114 CS)
- No impact of C-section delivery on respiratory outcomes:
  - Weekly respiratory symptoms
  - Weekly respiratory rate
  - Lung function at 6 weeks of age

Results // Respiratory symptoms

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VD: n=459 **CS**: n=111 (39 with CS planned)

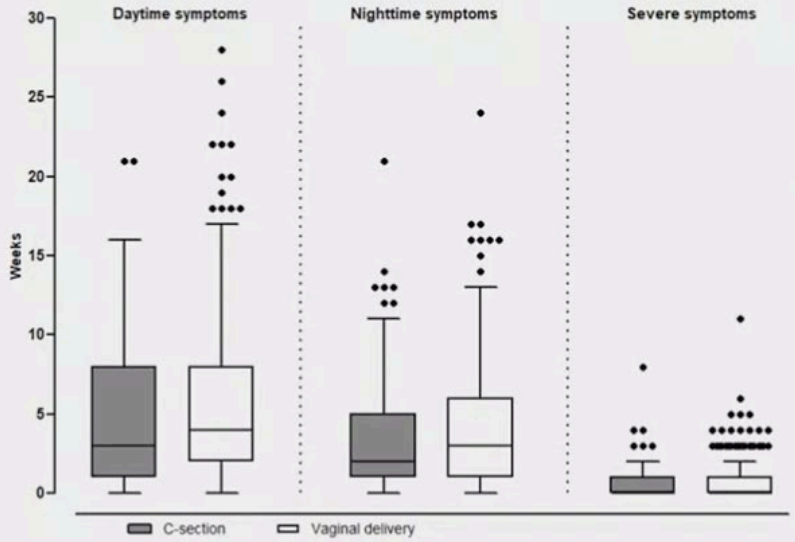

Figure 1. Weeks with respiratory symptoms in the first year of life.
Any day-/nighttime symptoms: score > 0. Any severe symptoms: score ≥ 3.

Association between mode of delivery and respiratory symptoms in the first year of life

Weeks with any respiratory symptoms	Adjusted IRR (95% CI) *	p value #
CS all	0.82 (0.67 to 0.998)	**0.048**
CS planned	0.75 (0.53 to 1.05)	0.09

Table 2. Weeks with any respiratory symptoms (symptom score > 0).
* adjusted for: sex, gestational age, birth weight, maternal age, older siblings, child care, atopy of the mother and the educational status of the father
# from poisson regression model with children born by VD as reference group

Sensor error in Eco Medics Exhalyzer D

ERS INTERNATIONAL CONGRESS 2020 virtual

Florian Wyler (Bern):

- 15-20% disagreement in outcomes between Ecomedics and ndd devices
- Due to sensor characteristics rather than algorithms or breathing pattern
- Ecomedics device over-estimates N_2 concentration due to error in O_2 sensor
- Correction is possible but will involve reloading all measurements (hopefully possible in future version of Spiroware – not 3.30)

Outcome differences in multiple-breath washout devices are explained primarily by sensor characteristics

Florian Wyler[1], Marc-Alexander Oestreich[1,2], Kathryn Ramsey[1], Philipp Latzin[1]

[1] Pediatric Respiratory Medicine, Inselspital, University Children's Hospital Bern, Switzerland
[2] Graduate School for Health Sciences, University of Bern, Switzerland

Background

Nitrogen multiple breath washout (MBW) is an established technique to assess ventilation inhomogeneity in the lungs.

Subjects inhale pure Oxygen and wash out the Nitrogen in their lungs until it drops below 1/40th of the initial concentration.

The main outcomes are the functional residual capacity (FRC) and lung clearance index (LCI).

Poor agreement between commercially available devices for MBW has been described, but it is not clear whether these differences are due to **breathing pattern**, **sensor characteristics**, or **outcome computation.**

Aims

We investigated differences in MBW outcomes due to

i) **sensors and signal processing** (e.g. measured/calculated gas-concentrations) and

ii) **computation of MBW outcomes**

between two commercial devices: **The Exhalyzer D** (eco; Ecomedics AG, Duernten, Switzerland), and **The EasyOne Pro Lab** (ndd; ndd Medizintechnik AG, Zurich, Switzerland).

Methods

Healthy adults (n=8) performed the MBW test into a modified flow head which allowed simultaneous measurement of side-stream sampled gas into both devices (Figure 1).

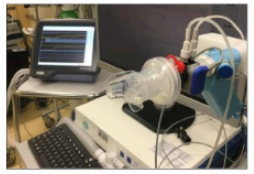

Figure 1: Illustration of the measurement setup, featuring the two side stream sample tubes. One of these belongs to the standard Ecomedcs setup, the other is a custom addition and feeds into the ndd device.

Methods

Simultaneous side-stream sampling provided us with the necessary signals to analyse measurements using both devices (Figure 2).

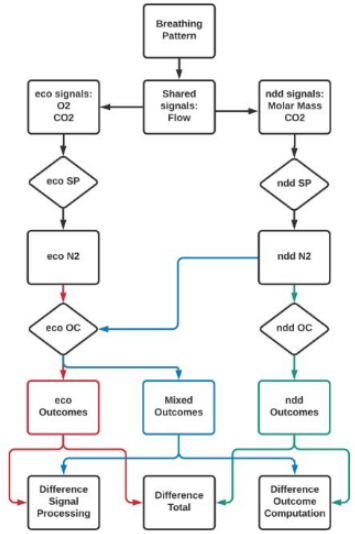

Figure 2: Overview of the analysis pipeline. SP = signal processing, OC = outcome computation

This setup made it possible to analyze device disagreements independently of breathing pattern or between-test variability.

Analyzing different nitrogen signals with the same software allowed us to calculate **the differences due to signal processing**.

Analyzing the same nitrogen signal in two different softwares allowed us to calculate the **difference due to outcome computation**.

Results

	Total difference (%)	Sensor characteristics (%)	Outcome computation (%)
LCI	**17.25 (7.02)**	18.10 (7.08)	-0.70 (2.05)
FRC	**13.34 (4.16)**	12.12 (3.98)	1.09 (1.25)

Table 1: Overview of the contribution of signal processing and outcome computation to total difference observed between devices. Mean (standard deviation).

Differences in sensor and signal processing steps accounted for the majority of the difference in outcomes between devices (Table 1).

Ecomedics systematically measures higher expiratory Nitrogen concentrations than ndd (see Figure 2).

Observed magnitude of differences in line with previous observations.

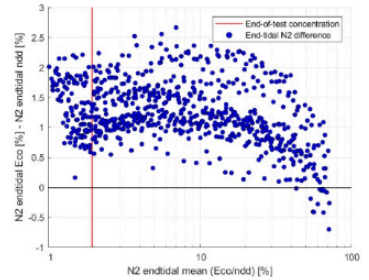

Figure 3: Overview of end-expiratory N2 concentration differences across all devices showing systematic sensor disagreement.

Conclusions

MBW outcomes across devices differ independently of breathing pattern.

Differences previously observed in MBW device outcomes can be attributed mainly to sensor characteristics.

Further work will investigate sensor accuracy and potential improvements for each device.

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Sensor error in Eco Medics Exhalyzer D

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Further development of SPIROWARE®

In the course of SPIROWARE® 3.3 development, we were informed by the Latzin group (Florian Wyler, Marc Oestreich, Kathryn Ramsey and Philipp Latzin) that the accuracy of our sensors can be further improved beyond the specifications from the manufacturer. We collaborated with them to extensively test the accuracy of the device sensors. Our measurements using a mass spectrometer confirmed the findings of the Latzin group who had used fixed reference gas mixtures. We have then developed an algorithm to correct the sensor signals (Fig. 1). In a first analysis we assumed a linear relationship and have re-analysed 884 N2MBW tests, which showed that the main effect was an offset and slight compression of the LCI scale. Z-scores remained stable on average (Fig. 2). At the moment, it looks like the clinical statement of the LCI remains the same.
Our goal is to implement an automatic correction, which can be applied during migration of the SPIROWARE® database. However further validation of the modified algorithms is required with a larger dataset.

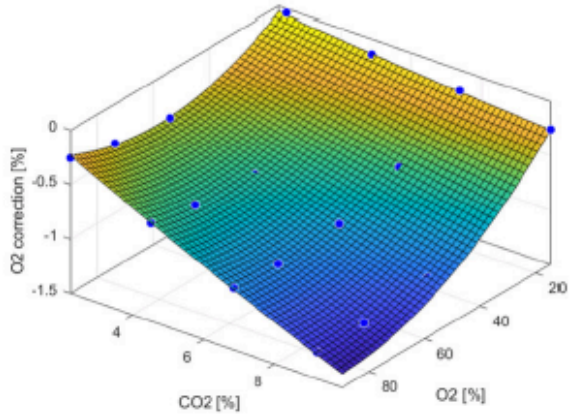

Fig. 1

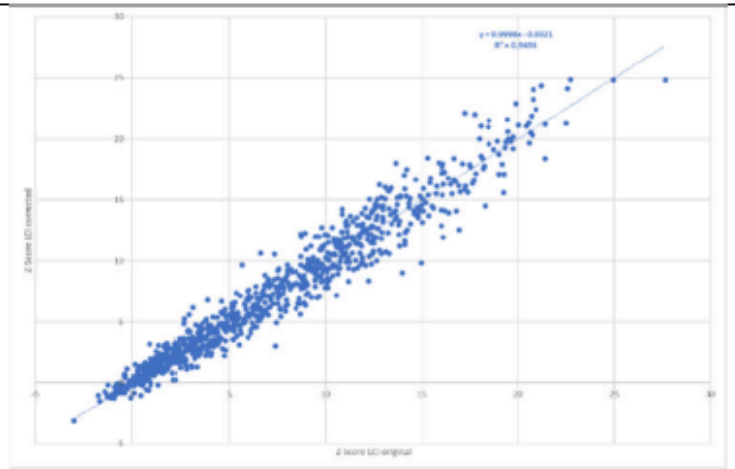

Fig. 2

New Wbreath version available online

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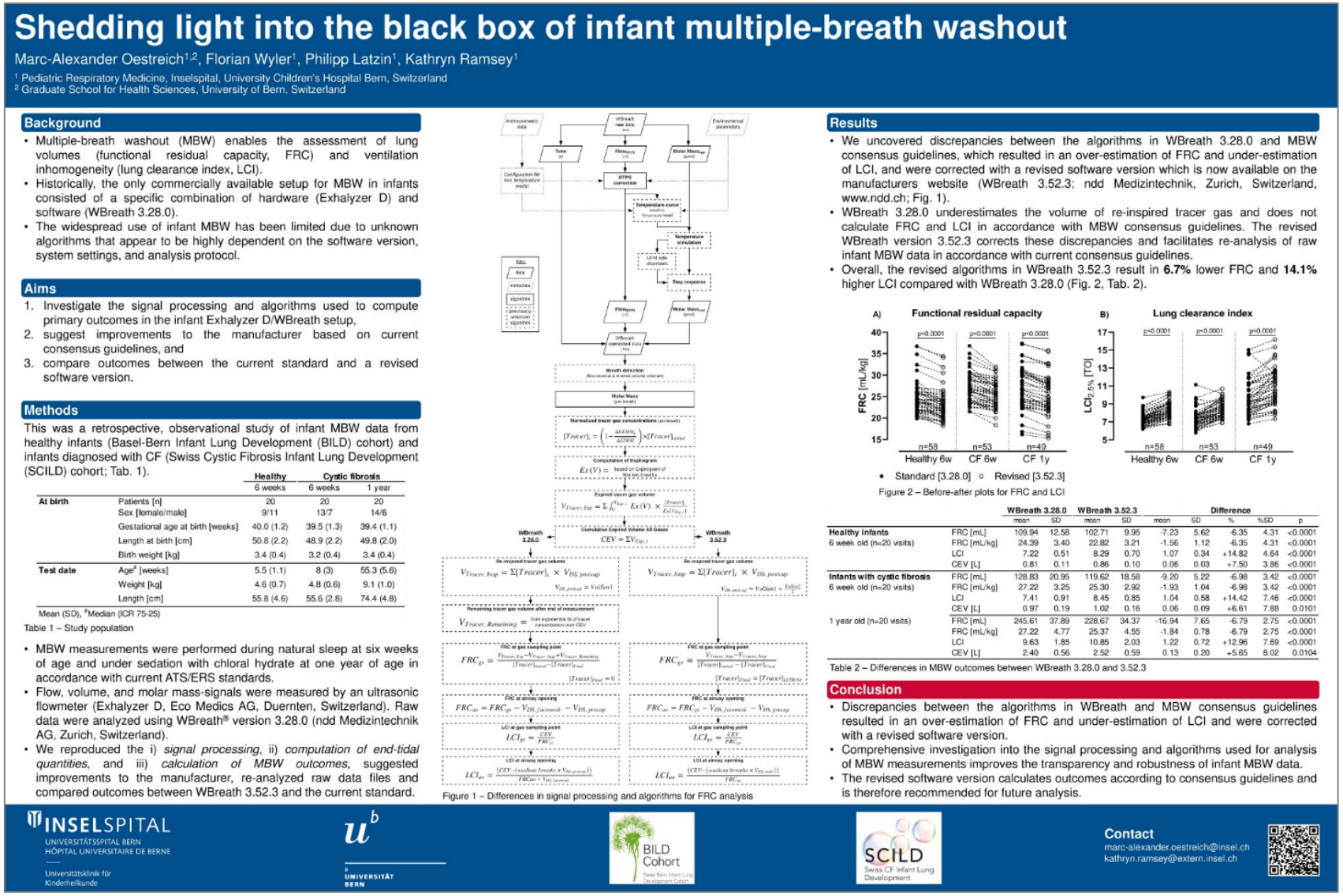
Marc Oestreich (Bern):

- Infant MBW signal processing and algorithms in current Wbreath version (3.28.0) unclear
- Large disagreement with new Spiroware setup
- Wbreath outcomes not calculated according to consensus statement
- New Wbreath version (3.52.3) uses same algorithms as consensus and Spiroware (available online)
- 15% increase in LCI and 7% decrease in FRC compared to old Wbreath version



Shedding light into the black box of infant multiple-breath washout

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Background

- Multiple-breath washout (MBW) enables the assessment of lung volumes (functional residual capacity, FRC) and ventilation inhomogeneity (lung clearance index, LCI).
- Historically, the only commercially available setup for MBW in infants consisted of a specific combination of hardware (Exhalyzer D) and software (WBreath 3.28.0).
- The widespread use of infant MBW has been limited due to unknown algorithms that appear to be highly dependent on the software version, system settings, and analysis protocol.

Aims

1. Investigate the signal processing and algorithms used to compute primary outcomes in the infant Exhalyzer D/WBreath setup,
2. suggest improvements to the manufacturer based on current consensus guidelines, and
3. compare outcomes between the current standard and a revised software version.

Methods

This was a retrospective, observational study of infant MBW data from healthy infants (Basel-Bern Infant Lung Development (BILD) cohort) and infants diagnosed with CF (Swiss Cystic Fibrosis Infant Lung Development (SCILD) cohort; Tab. 1).

		Healthy	Cystic fibrosis	
		6 weeks	6 weeks	1 year
At birth	Patients [n]	20	20	20
	Sex [female/male]	9/11	13/7	14/6
	Gestational age at birth [weeks]	40.0 (1.2)	39.5 (1.3)	39.4 (1.1)
	Length at birth [cm]	50.8 (2.2)	48.9 (2.2)	49.8 (2.0)
	Birth weight [kg]	3.4 (0.4)	3.2 (0.4)	3.4 (0.4)
Test date	Age[#] [weeks]	5.5 (1.1)	8 (3)	55.3 (5.6)
	Weight [kg]	4.6 (0.7)	4.8 (0.6)	9.1 (1.0)
	Length [cm]	55.8 (4.6)	55.6 (2.8)	74.4 (4.8)

Mean (SD), [#]Median (ICR 75-25)

Table 1 – Study population

- MBW measurements were performed during natural sleep at six weeks of age and under sedation with chloral hydrate at one year of age in accordance with current ATS/ERS standards.
- Flow, volume, and molar mass-signals were measured by an ultrasonic flowmeter (Exhalyzer D, Eco Medics AG, Duernten, Switzerland). Raw data were analyzed using WBreath® version 3.28.0 (ndd Medizintechnik AG, Zurich, Switzerland).
- We reproduced the i) *signal processing*, ii) *computation of end-tidal quantities*, and iii) *calculation of MBW outcomes*, suggested improvements to the manufacturer, re-analyzed raw data files and compared outcomes between WBreath 3.52.3 and the current standard.

Figure 1 – Differences in signal processing and algorithms for FRC analysis

Results

- We uncovered discrepancies between the algorithms in WBreath 3.28.0 and MBW consensus guidelines, which resulted in an over-estimation of FRC and under-estimation of LCI, and were corrected with a revised software version which is now available on the manufacturers website (WBreath 3.52.3; ndd Medizintechnik, Zurich, Switzerland, www.ndd.ch; Fig. 1).
- WBreath 3.28.0 underestimates the volume of re-inspired tracer gas and does not calculate FRC and LCI in accordance with MBW consensus guidelines. The revised WBreath version 3.52.3 corrects these discrepancies and facilitates re-analysis of raw infant MBW data in accordance with current consensus guidelines.
- Overall, the revised algorithms in WBreath 3.52.3 result in **6.7%** lower FRC and **14.1%** higher LCI compared with WBreath 3.28.0 (Fig. 2, Tab. 2).

Figure 2 – Before-after plots for FRC and LCI

		WBreath 3.28.0		WBreath 3.52.3		Difference				
		mean	SD	mean	SD	mean	SD	%	%SD	p
Healthy infants	FRC [mL]	109.94	12.58	102.71	9.95	-7.23	5.62	-6.35	4.31	<0.0001
6 week old (n=20 visits)	FRC [mL/kg]	24.39	3.40	22.82	3.21	-1.56	1.12	-6.35	4.31	<0.0001
	LCI	7.22	0.51	8.29	0.70	1.07	0.34	+14.82	4.64	<0.0001
	CEV [L]	0.81	0.11	0.86	0.10	0.06	0.03	+7.50	3.86	<0.0001
Infants with cystic fibrosis	FRC [mL]	128.83	20.95	119.62	18.58	-9.20	5.22	-6.98	3.42	<0.0001
6 week old (n=20 visits)	FRC [mL/kg]	27.22	3.25	25.30	2.92	-1.93	1.04	-6.98	3.42	<0.0001
	LCI	7.41	0.91	8.45	0.85	1.04	0.58	+14.42	7.46	<0.0001
	CEV [L]	0.97	0.19	1.02	0.16	0.06	0.09	+6.61	7.88	0.0101
1 year old (n=20 visits)	FRC [mL]	245.61	37.89	228.67	34.37	-16.94	7.65	-6.79	2.75	<0.0001
	FRC [mL/kg]	27.22	4.77	25.37	4.55	-1.84	0.78	-6.79	2.75	<0.0001
	LCI	9.63	1.85	10.85	2.03	1.22	0.72	+12.96	7.69	<0.0001
	CEV [L]	2.40	0.56	2.52	0.59	0.13	0.20	+5.65	8.02	0.0104

Table 2 – Differences in MBW outcomes between WBreath 3.28.0 and 3.52.3

Conclusion

- Discrepancies between the algorithms in WBreath and MBW consensus guidelines resulted in an over-estimation of FRC and under-estimation of LCI and were corrected with a revised software version.
- Comprehensive investigation into the signal processing and algorithms used for analysis of MBW measurements improves the transparency and robustness of infant MBW data.
- The revised software version calculates outcomes according to consensus guidelines and is therefore recommended for future analysis.

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BILD Cohort

SCILD Swiss CF Infant Lung Development

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Summary of Spirometry data in Africa

R Masekela and Diane Gray

Inclusion flowchart for total PAAS study

Smith S-J, Gray DM, MacGinty R et al **Choosing the Better GLI2012 Equation in South African Population Groups** AJRCCM Articles in Press. Published August 06, 2020 as 10.1164/rccm.202005-2085LE

PAAS 2- Results

Table 1. Characteristics of the study population (KwaZulu-Natal and Western Cape province, South Africa).

	Black African (n=2116)	Caucasian (n=343)	Mixed Ethnicity (n=693)	Indian (n=524)	Total (n=3676)
Sex - Female	1200 (56.6%)	153 (44.6%)	404 (58.3%)	326 (62.2%)	2083 (56.7%)
Age					
< 25 years	1128 (53.3%)	212 (61.8%)	440 (63.5%)	243 (46.4%)	2023 (55.0%)
>25 years	988 (46.7%)	131 (38.2%)	253 (36.5%)	281 (53.6%)	1653 (45.0%)
Weight for age Z-score	0.04 (0.41)	0.10 (0.66)	0.09 (0.47)	0.12 (0.56)	0.07 (0.48)
Height for age Z-score	-0.27 (0.84)	0.08 (0.87)	-0.40 (1.12)	-0.25 (0.95)	-0.26 (0.92)
BMI for age Z-score	0.99 (1.28)	0.71 (1.15)	0.90 (1.034)	1.01 (1.28)	0.95 (1.29)
Cormic index	0.51 (0.03)	0.52 (0.04)	0.50 (0.03)	0.52 (0.03)	0.51 (0.03)
Stunting*	110 (5.2%)	5 (1.5%)	64 (9.2%)	37 (7.1%)	216 (5.9%)
Province					
KwaZulu-Natal	1260 (59.6%)	236 (68.8%)	306 (44.2%)	517 (98.7%)	2319 (63.1%)
Western Cape	856 (40.4%)	107 (31.2%)	387 (55.8%)	7 (1.3%)	1357 (36.9%)

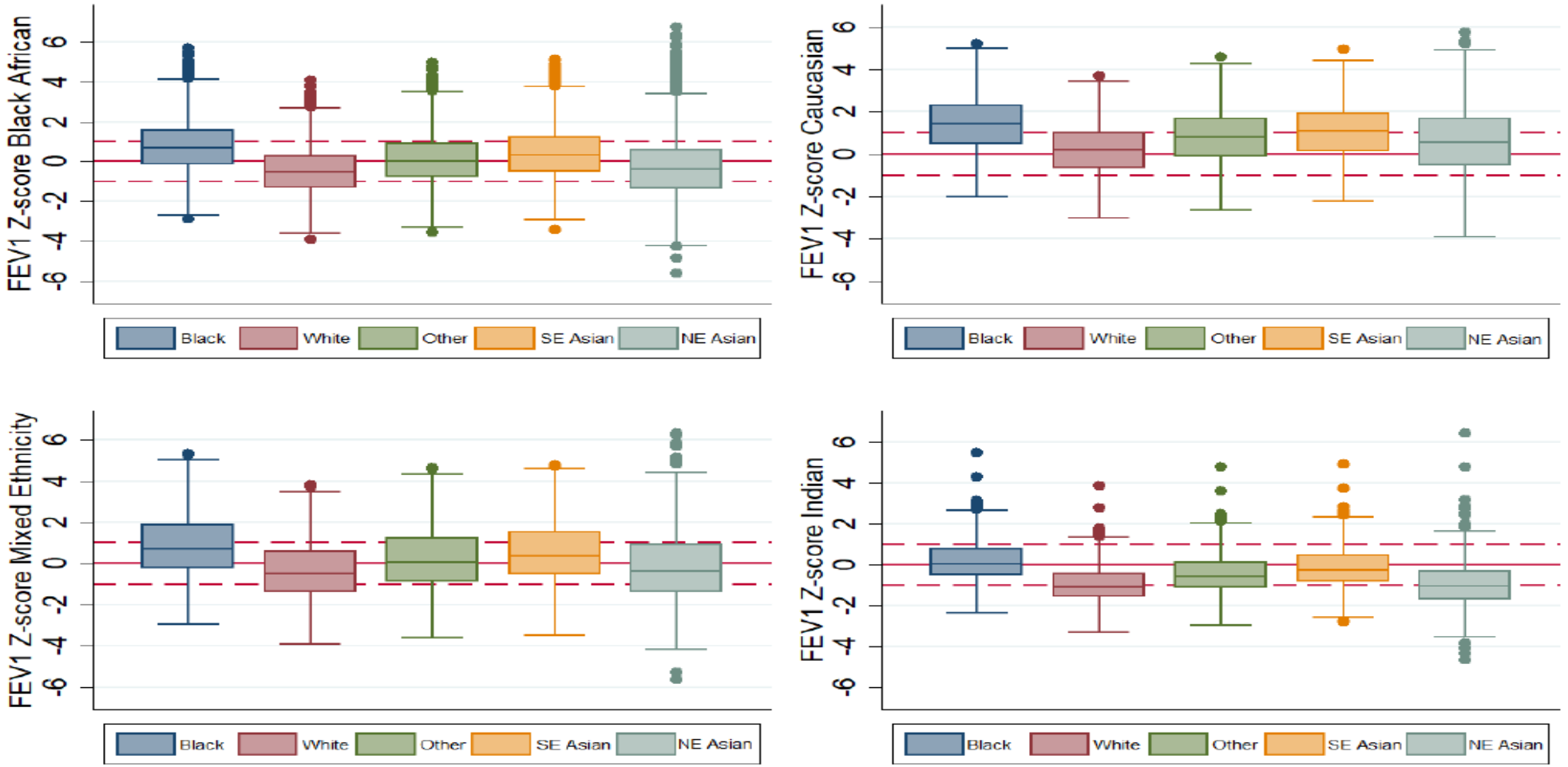

Figure 2. Summary of FEV_1 Z-scores for each ethnic group using each of the GLI reference equations. The equations that resulted in the closest fit to a mean z-score of zero, and a standard deviation of one were selected as best fit.

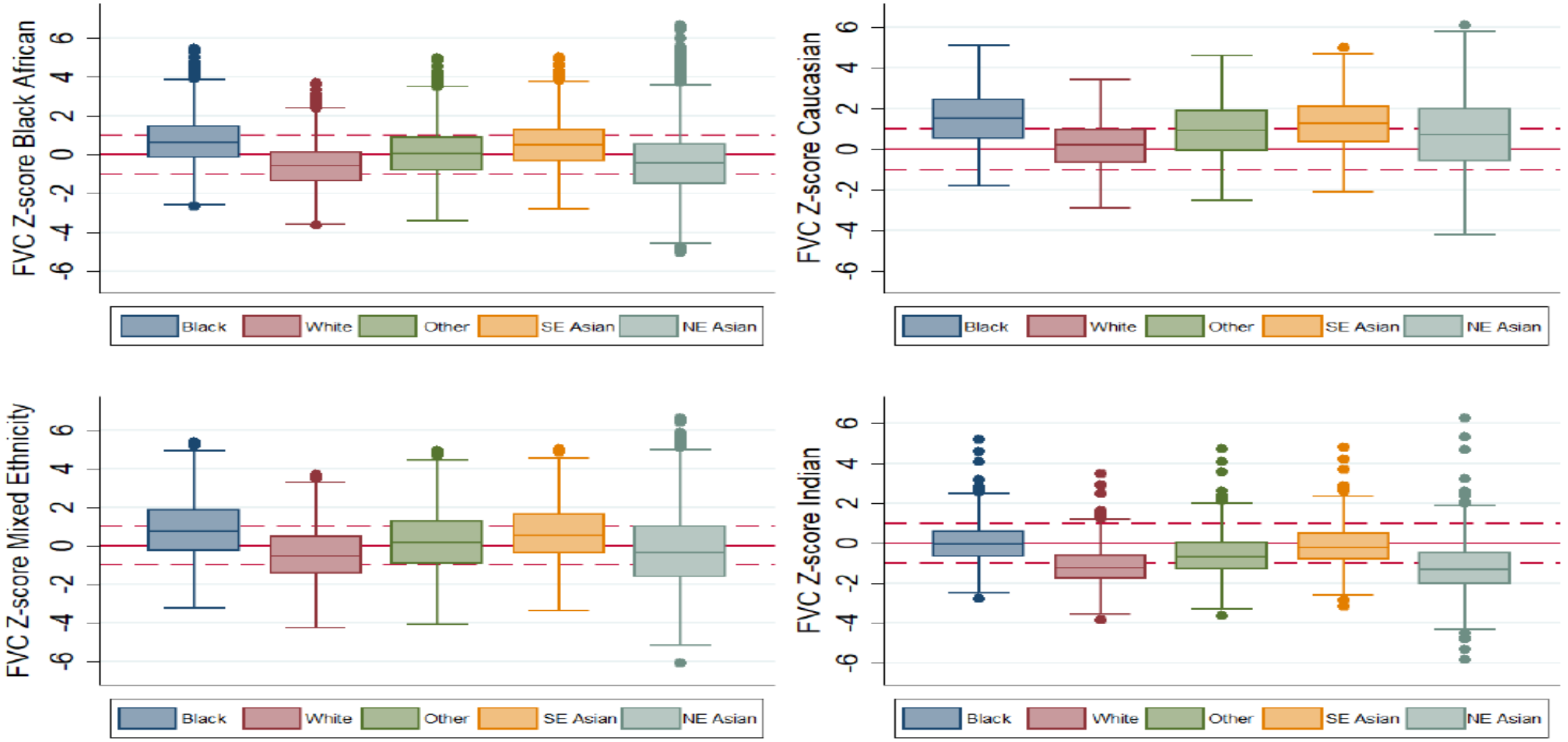

Figure 3. Summary of FVC Z-scores for each ethnic group using each of the GLI reference equations. The equations that resulted in the closest fit to a mean z-score of zero, and a standard deviation of one were selected as best fit.

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