

Congenital Disorders Surveillance in Africa: Western Cape Pregnancy Exposure Registry

Emma Kalk
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Congenital Disorders in South Africa

- No reliable background rates of congenital disorders in SA
(Lawn Lancet 2016; Lebeso SAMJ 2006)
- South Africa: mass treatment campaigns for HIV & TB
- Pregnant women are exposed to new medicines with little data on pregnancy effects (e.g. dolutegravir, 2nd line TB agents) & known medicines with proven teratogenic effects (e.g. sodium valproate)
- Can't rely on post-licensing spontaneous reporting
- Need for a sustainable surveillance programme of pharmacovigilance during pregnancy (& breastfeeding)
 - Collect routine clinical data on pregnancy exposures and maternal & fetal/infant outcomes



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Western Cape Pregnancy Exposure Registry (PER)

- Sentinel-site based population registry
- Enrolment at primary care antenatal facilities
 - Gugulethu Midwife Obstetric Unit in Cape Town (2016 – present)
 - Worcester Midwife Obstetric Unit in Breede Valley (2018 – 2019)
- All women attending antenatal care: denominator
- Follow from enrolment to pregnancy outcome regardless of site
- Embedded in routine services, including data collection software
- Digitize routine medical records
- Electronic health information exchange



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Principles of Pregnancy Surveillance

- Robust data collection of exposures and outcomes (data quality & completeness)
- Standardised methods & definitions
 - External surface examination of neonate/stillbirth
 - WHO
 - ICD-10 codes
- Population coverage
 - Sentinel-site based
 - Geographic areas serviced by the sentinel site/s
 - Primary care obstetric facility enrolment
 - Antenatal enrolment – prospective
 - All women attending antenatal care - denominator
 - Not hospital-based



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Principles of Pregnancy Surveillance

- Integrated into routine systems (clinical and data platforms)
 - Service provision (versus research)
 - Avoid parallel systems
 - Embedded data staff
 - Existing government sector software
 - Digitizing routinely-collected data (no additional fields)
 - Systems strengthening to improve clinical care & clinical record-keeping
 - Data are automatically integrated into Provincial data management systems
 - Data are incorporated into reporting



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Western Cape Province, South Africa



- Southernmost of South Africa's 9 provinces
- Population: 7.4 million (12% national pop)
- Cape Town Metro municipality: 4.8 million
- Private medical scheme coverage: 23.9%
- HIV prevalence: 8.2%
- Antenatal HIV prevalence: 16.3%
- Obstetric care is free in government sector
- Antenatal visit coverage: 78.6%
- In-facility delivery
- Electronic health data collection systems



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Gugulethu, Western Cape



- 15km from centre of Cape Town
- Population: >98,000 (2011)
- Historically black African
- Mixed formal & informal housing
- High unemployment
- Antenatal HIV prevalence: ~30%
- Obstetric care: City of CT clinics, Midwife Obstetric Unit, District Hospital, Mowbray Maternity Hospital, Groote Schuur Hospital (tertiary)

Breede Valley, Western Cape



- 120km from Cape Town
- Population: 127,597 (2020)
- Farming communities
- Mixed formal & informal housing
- Seasonal employment
- Antenatal HIV prevalence: ~14%
- Obstetric care: ANC clinics, Midwife Obstetric Unit, District Hospital, Karl Bremer Hospital, Tygerberg Hospital (tertiary)



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Obstetric Services and Registers

- Antenatal and delivery services free in public health sector
- Dating ultrasound < 22 weeks gestation (~30% at Gugulethu)
- Referral pathway for ante/perinatal complications
- Neonatal and adult ICU
- At the tertiary hospitals:
 - Fetal Medicine Unit
 - Medical Genetics services
 - Neurosurgery
 - Cardiac surgery
 - Plastic surgery (orofacial clefts)
 - Paediatric surgery



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PER: methodology



CONGENITAL DISORDER
Folder review

Methods

MATERNITY CASE RECORD

ROUTINE CLINICAL RECORDS

Ward stock dispensing
Vaccinations
Alcohol, tobacco & recreational drugs (OTC, traditional medicines)
Medical conditions & treatment



ELECTRONIC PHARMACY DISPENSING

validate



LAB & DIAGNOSTICS



HIV&TB DISEASE INFORMATION SYSTEMS

MATERNITY CASE RECORD

Gestational age, birth anthropometry
Examination of neonate/stillbirth

ROUTINE CLINICAL RECORDS



PHDC

Cohort: women present for antenatal care at primary care site (midwife obstetric unit)

Pregnancy outcome, including pregnancy loss, at delivery site: primary care; district, secondary, tertiary hospitals

EXPOSURE ASCERTAINMENT

OUTCOME ASCERTAINMENT



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Provincial Health Data Centre

Patient seeks health care, folder is retrieved or created



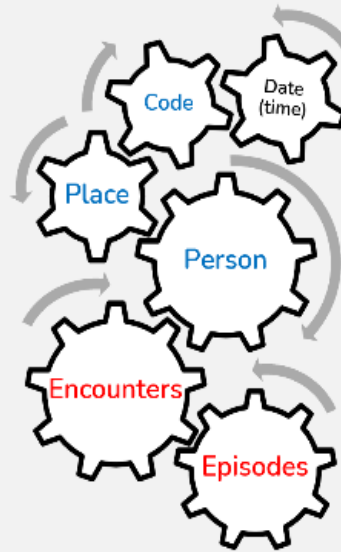
Folder number used on all records



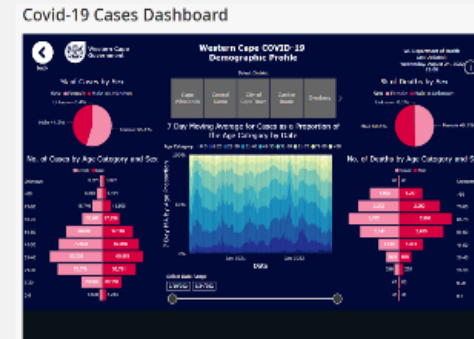
Patient-level health records captured into routine information systems



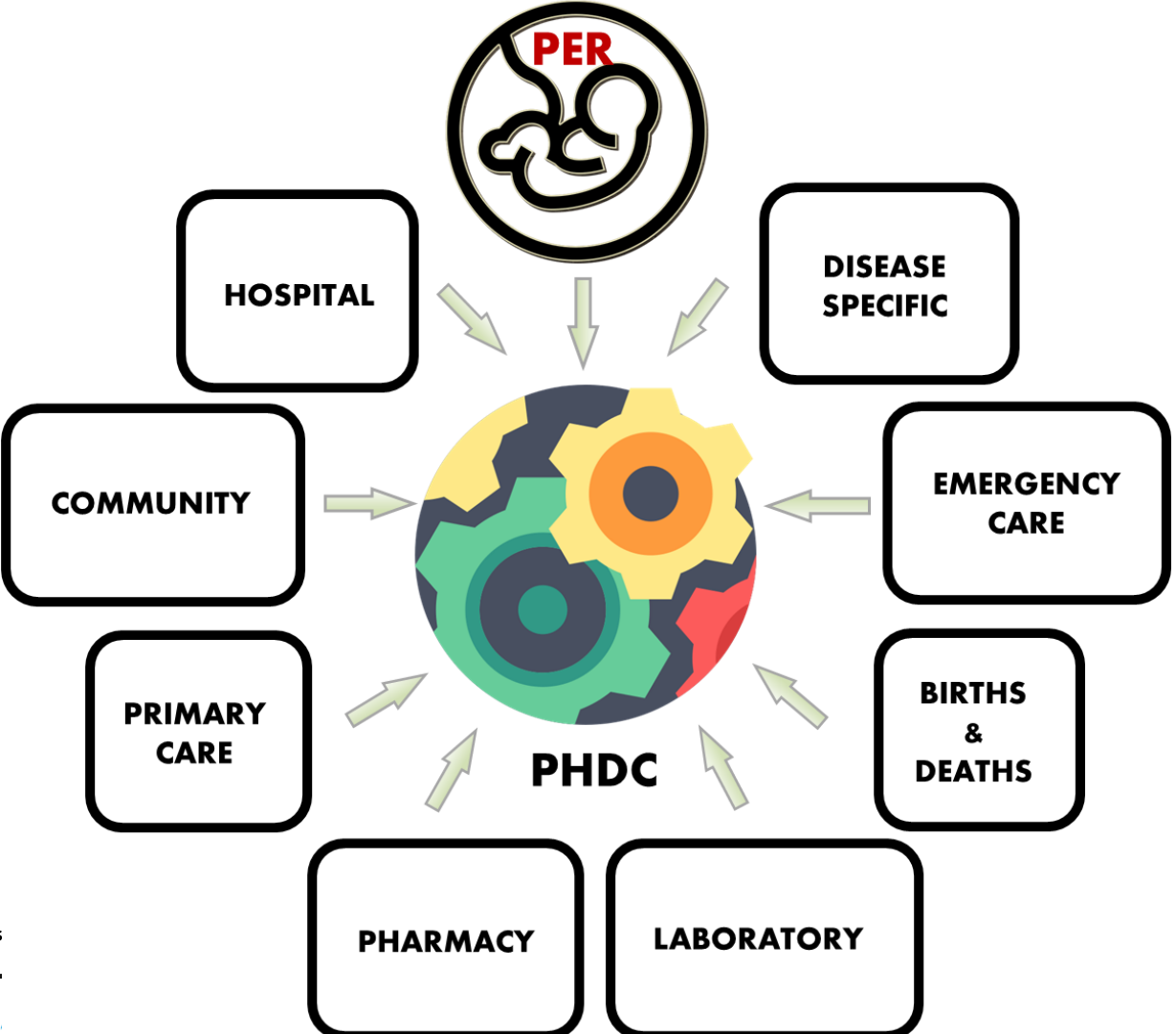
Data Centre retrieves data from source systems and consolidates and makes inference



Actionable reports, dashboards and patient management tools accessible to those responsible for patient follow up & datasets available for analyses



PER: methodology



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(Boulle et al., IJPS 2019)



PER: validation

Indicator 2018 - 2019	PER total n = 14 527	PER urban n = 9435 (65%)	PER rural n = 5092 (35%)	Reported aggregate for the Western Cape 2017 - 2019 ^a
Still birth ^b n (%)	296 (2.0)	180 (1.9)	116 (2.4)	2.2% ²⁶
Per 1000 births	20.0	19.1	24.0	18.5 ¹⁷ 22.1 ^{25,26}
Neonatal death in facility rate ^c per 1000 live births	8.7	9.2	7.7	8.9 ^{17,25}
Perinatal mortality rate ^d per 1000 births	29	29	29	25.6 ¹⁷ 27.9 ²⁵ 29.1 ²⁶
Low birth weight ^e n(%)	1737 (12.0)	879 (9.3)	857 (16.8)	14.9% urban subdistrict 18.4% rural subdistrict ²⁶
Maternal mortality in facility ratio per 100 000 live births		63.5	Insufficient data	43.6 – 66.8 ²⁵
Teenage pregnancies (10 – 19 years) n(%)	929 (6.4)	450 (4.8)	497 (9.4)	3.5% urban subdistrict 7.3% rural subdistrict ²⁶
Caesarean section rate per 1000 births	3416 (26.6)	2411 (30.0)	1005 (21.0)	28.9 ²⁵ - 29.3 ²⁶

Validated pregnancy outcomes
against DHIS
(Kalk et al., *BMJ Open* 2022)

Validated PHDC definitions against
the more granular data in the PER
(Slogrove Aet al., *13th International Workshop on HIV Pediatrics*. 29 September-7 October 2021)

Overview of Pregnancies in the Western Cape

Pregnancy outcome date range: 2016/09/01 - 2023/12/31

Filters:

Province wide
Other filters: „ Only PER (Pregnancy Exposure Registry) patients included

Maternal Cascade

35780
Live births

91.7%
Live births (%)

39013
Pregnancies

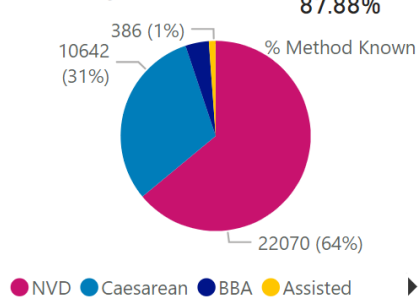
28
Maternal deaths

4525
Teen pregnancies

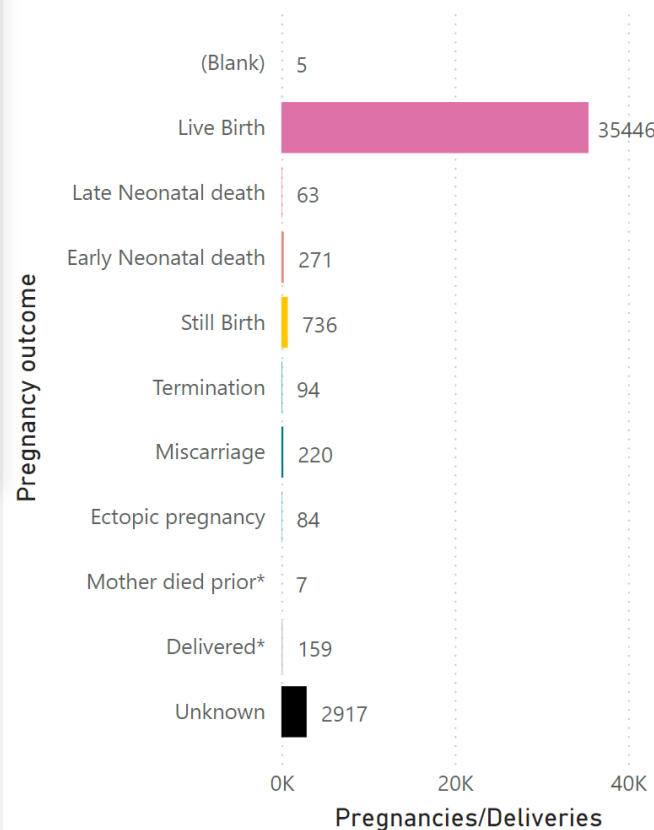
Notes

Pregnancies and outcomes are inferred based on evidence gathered from electronic health systems. Only high confidence pregnancies are included in this report. Maternal deaths are ascertained from in facility deaths and deaths captured into Sinjani. Maternal deaths are not restricted to live births, and women who died during pregnancy without an outcome are also included. The "delivered" outcome means there is evidence of delivery (e.g. diagnosis or procedure code), but the vital status of the infant is unknown

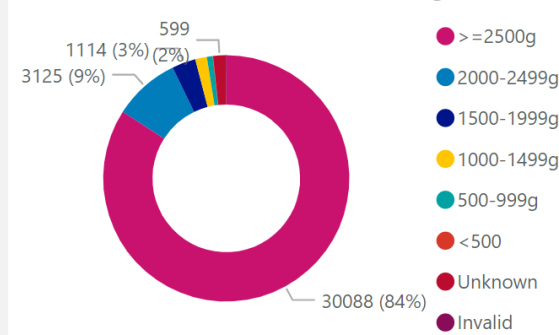
Delivery method



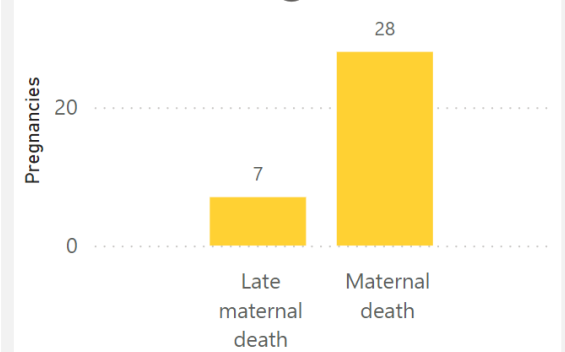
Pregnancies by Outcomes



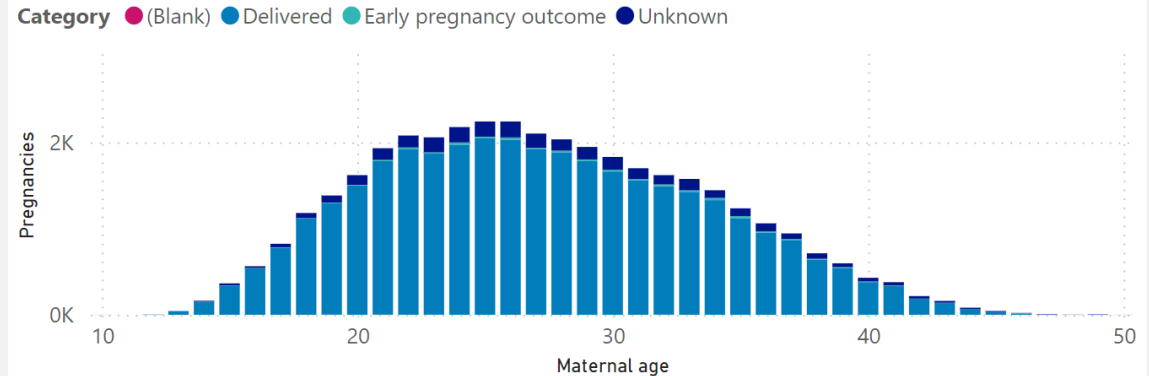
Birth weight for Live births



Maternal deaths



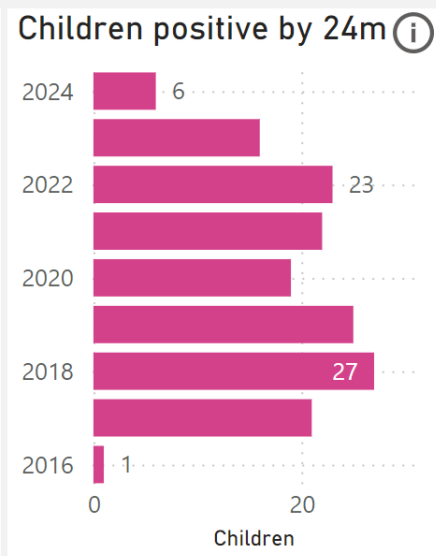
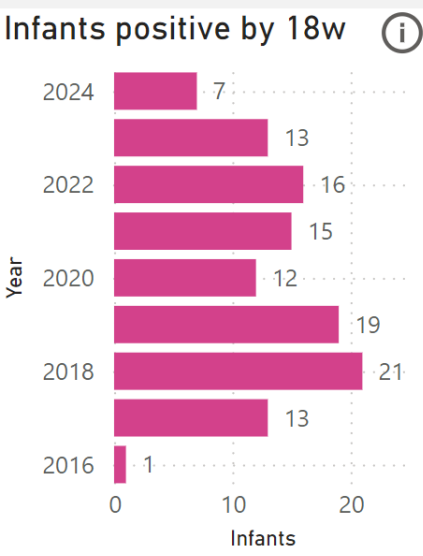
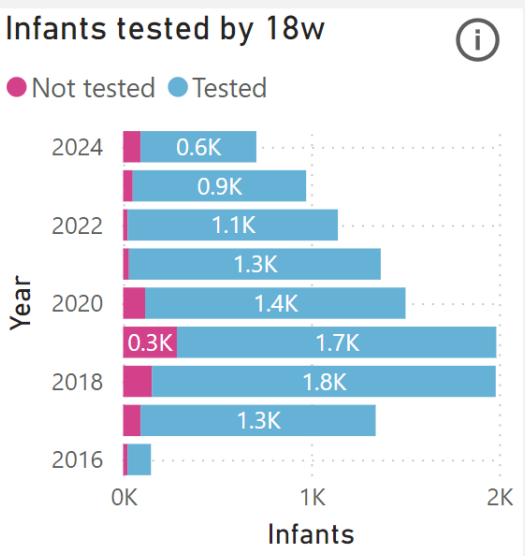
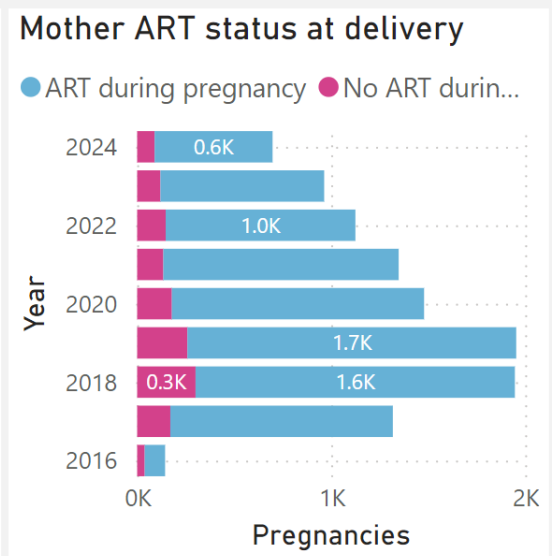
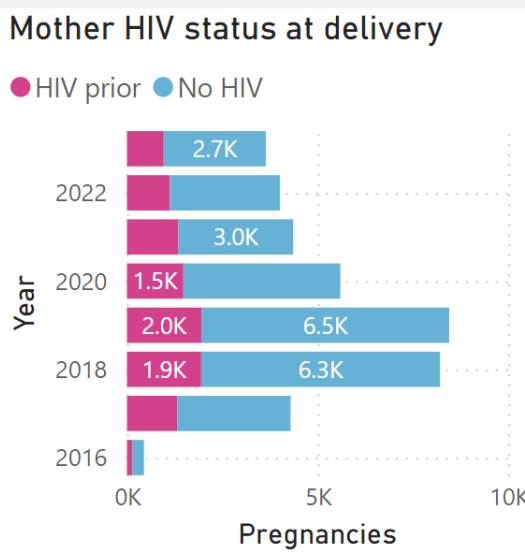
Pregnancies by Age and Outcome category



Maternal Cascade

Pregnancy outcome date range: 2016/09/01 - 2023/12/31

<p>Mothers with HIV known at delivery of all live births</p> <p>29.76%</p>	<p>Mothers who received ART during pregnancy of those with known HIV status</p> <p>86.86%</p>	<p>Infants tested by 18 weeks of all live births to WLWHIV</p> <p>91.48%</p>	<p>Infants tested positive by 18 weeks of all those tested</p> <p>1.14%</p>	<p>Children tested positive by 24 months of all live births to WLWHIV</p> <p>1.45%</p> <p><small>*Only including infants linked to mothers</small></p>
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Congenital Disorders in the PER

- Routine electronic health data in the WC Pregnancy Exposure Registry
- Women with a viable pregnancy: >22 weeks' gestation/birth weight $\geq 500\text{g}$
- Congenital Disorders:
 - neonatal surface examination
 - ICD-10 coding in the electronic data
 - Confirmed by folder review
- Compared with antenatal diagnosis at Fetal Medicine Unit
- Assess late diagnosis (up to 2 years old)
- Associations



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Congenital Disorders in the PER

- Neonatal surface examination at birth = standard of care *(Holmes, et al. BDR. 2021)*
- Within 24 hours of birth
- Major external anomalies
- Cyanotic congenital heart defects
- Critical congenital heart defects
- Congenital cataract
- Imperforate anus
- Intestinal atresias



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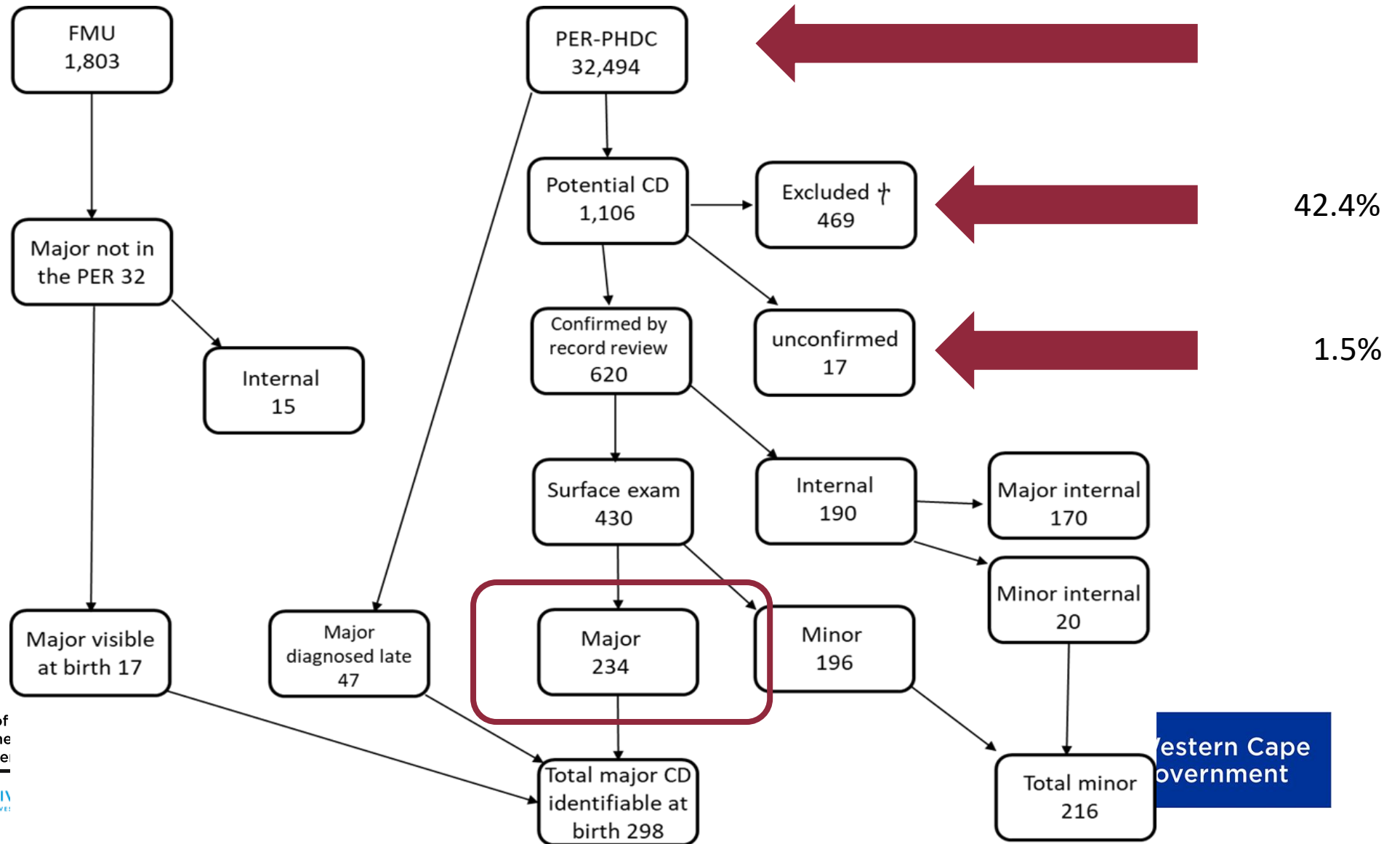


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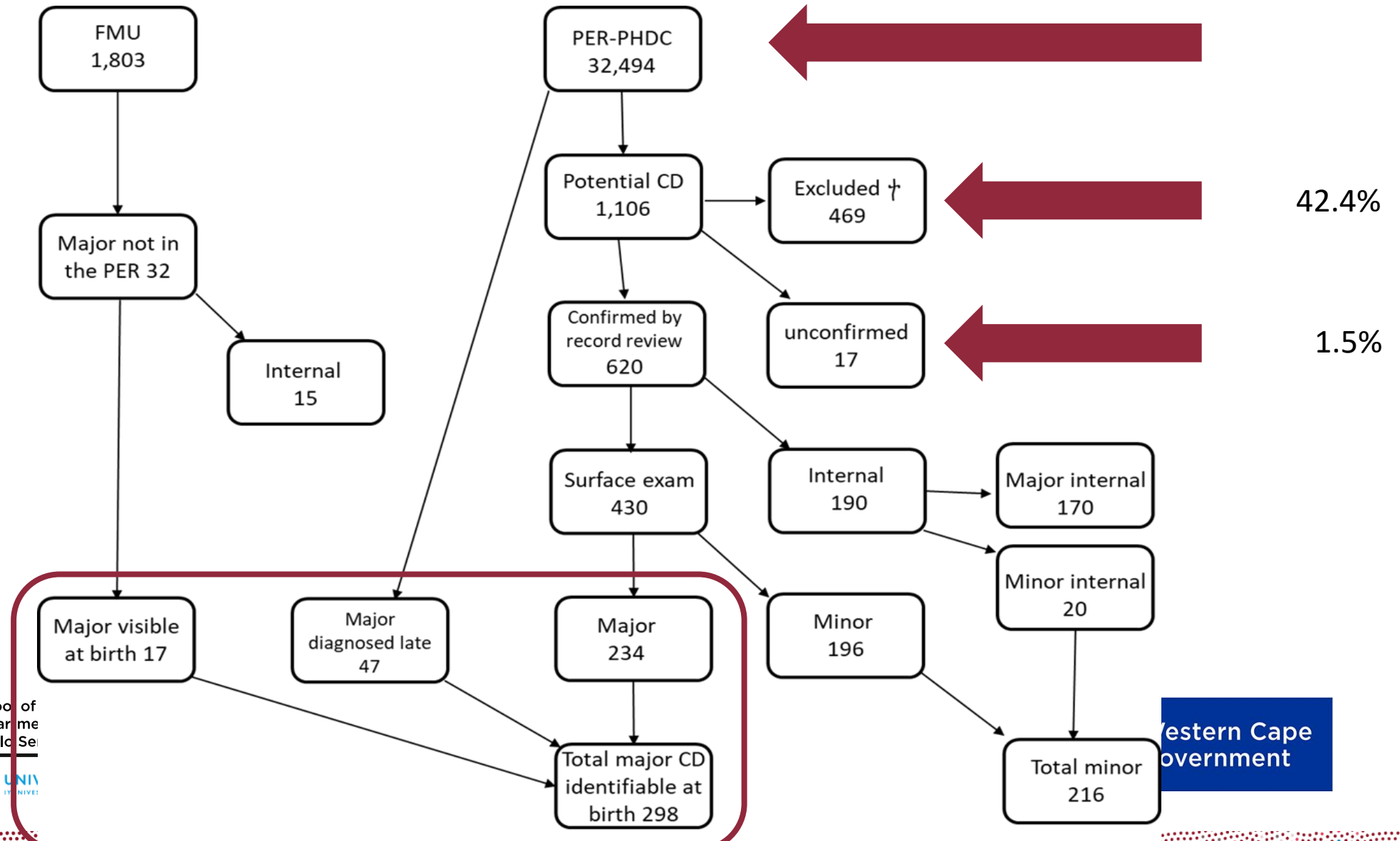


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Congenital Disorders in the PER



Associations with Congenital Disorders

- Women with pregnancies affected by congenital disorders were associated with:
 - Older age: 28.8y (IQR 23.5-35.6) versus 27.2y (22.7-32.3)
 - Previous adverse pregnancy outcome (24.5% versus 19%)
 - Gestational diabetes
 - Receipt of an antenatal ultrasound
 - Delivery in hospital versus primary care
 - Prematurity
 - Low birth weight
 - Stillbirth versus livebirth
 - Neonatal death
- Women with pregnancies affected by congenital disorders were NOT associated with:
- HIV, timing or ART, gestational age at 1st antenatal visit, hypertension, obesity, alcohol (gets close), recreational drugs (numbers low)



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Congenital Disorders in the PER

Major congenital disorders

47 missed at external examination at birth - diagnosed late (16.8%)

17 seen on US but not reported at external examination at birth (6.8%)

	Number	Prevalence/1000 births	Prevalence/1000 livebirths	Prevalence/1000 stillbirths
PER only	234	7.2	7.2	10.8
PER + FMU + missed	298	9.2	8.9	21.5
External + internal	558	17.2		
Post-axial polydactyly Type B	180	5.5		



Congenital Disorders in the PER

Diagnosed late (>24h) 16.8%

Condition	Number	Median age (IQR)
Down Syndrome	13	60 (45-156) days
Hypospadias	6	51.5 (45-80)
Cervical meningocoele	1	90
Anorectal malformation	3	3
[isolated cleft palate]	2	5-120

On ultrasound only 6.8%

Condition	Number	Outcome
Trisomy 18	1	Stillbirth
Chromosomal abn NOS	2	Stillbirth
Omphalocele	1	Stillbirth
Skeletal dysplasia NOS	5	3 Stillbirth; 1 NND; 1 Livebirth
Congenital syphilis	1	Stillbirth
Cleft lip & palate	1	Livebirth
Amniotic band syndr.	1	Livebirth



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Congenital Disorders in the PER – regional comparisons

Major external congenital disorders

Neonatal surface examination

All major

	Number	Prevalence/1000 births	Prevalence/1000 livebirths	Prevalence/1000 stillbirths
PER only	234	7.2	7.2	10.8
PER + FMU + missed	298	9.2	8.9	21.5
Tsepamo (Botswana)		6.0		
Eswathini		8.0		
Malawi		3.6		
KwaZulu-Natal, South Africa		5.0		
South Africa modelled		27.6		
EUROCAT		27.0		
NCARDS (UK)		22.3		



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(Zash et al., NEJM 2019; Gill et al., OFID 2023; Bello et al., AIDS2022; Mehta et al., SAJHIVM 2019; Malherbe et al., 2022; Broughan et al., 2024)

Congenital Disorders in the PER – regional comparisons

Major congenital disorders/1000 births

	WC PER	Tsepamo	eSwathini	Malawi	Uganda	South Africa modelled	South Africa 2008
Chromosomal	1.9					1.8	
Trisomy 21	1.4					1.7	
Trisomy 18	0.25						
Neural Tube Defects	0.52	0.7	0.8	0.57	0.98	1.2	0.98
Orofacial clefts	0.43	0.4				0.9	0.39
Gastrointestinal tract	0.64	0.5					0.46
Genito-urinary tract	1.8	0.1					
Musculoskeletal	1.1						
Skeletal dysplasia	0.18	0.2					
Talipes equinovarus	0.34	1.8		1.7			



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(Zash et al., NEJM 2019; Gill et al., OFID 2023; Bello et al., AIDS2022; Malherbe et al., 2022; Sayed et al., 2008; Barlow-Mosha et al., 2022)

Teratogen Exposure

Total prevalence teratogen exposure: 0.34/1000 births

	Number		Prevalence/1000 births
	Livebirth	Stillbirth	
Fetal Alcohol Spectrum Disorder	5	0	0.15
Valproate embryopathy	1	0	0.03
Congenital CMV syndrome	4	0	0.12
Congenital syphilis	1	1	0.06
Diabetes mellitus	16	3	0.58



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Western Cape PER: challenges

- Dependence on routine data collection
 - missing and incomplete data
 - System strengthening
- Enormous advantage being integrated into the PHDC – exposure & outcome ascertainment (linkage)
- Size and scope of the population

- Limitations of the external surface examination of the neonate/stillbirth
- Depends on definitions
- Depends on the question
- Funding



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