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Prevalence, geographical distribution and factors associated with pentavalent vaccine zero dose status among children in Sindh, Pakistan: analysis of data from the 2017 and 2018 birth cohorts enrolled in the provincial electronic immunisation registry

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ABSTRACT

Objectives To estimate the prevalence of zero dose children (who have not received any dose of pentavalent (diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B and hepatitis B) vaccine by their first birthday) among those who interacted with the immunisation system in Sindh, Pakistan along with their sociodemographic characteristics and risk factors.

Design and participants We conducted a descriptive analysis of child-level longitudinal immunisation records of 1 467 975 0–23 months children from the Sindh's Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry (ZM-EIR), for the birth cohorts of 2017 and 2018.

Setting Sindh province, Pakistan which has a population of 47.9 million people and an annual birth cohort of 1.7 million.

Primary and secondary outcome measures The primary outcome measure was zero dose status among enrolled children. Logistic regression was performed to identify the risk factors associated with the zero dose status.

Results Out of 1 467 975 children enrolled in the ZM-EIR in Sindh, 10.6% (154 881/1 467 975) were zero dose. There were sharp inequities across the 27 districts. Zero dose children had a lower proportion of hospital births (28.5% vs 34.0%; difference 5.5 percentage points (pp) (95% CI 5.26 to 5.74); p<0.001) and higher prevalence from slums (49.5% vs 42.3%; difference 7.2 pp (95% CI 6.93 to 7.46); p<0.001), compared with non-zero dose children. Children residing in urban compared with rural areas were at a higher risk (relative risk (RR): 1.20; p<0.001; 95% CI 1.18 to 1.22), while children with educated compared with uneducated mothers were at a lower risk of being zero dose (RR: 0.47–0.96; p<0.001; 95% CI 0.45 to 0.98).

Conclusions Despite interacting with the immunisation system, 1 out of 10 children enrolled in the ZM-EIR in Sindh were zero dose. It is crucial to monitor the prevalence of zero dose children and investigate their characteristics and risk factors to effectively reach and follow-up with them.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study analysed big data of 1.4 million children extracted from 5.4 million child-level longitudinal immunisation records in provincial Electronic Immunisation Registry (EIR) across Sindh.
⇒ Large granular data collected by the EIR has allowed analysis of the inequity in zero dose prevalence at a microgeographic level.
⇒ The study results can only be generalised to zero dose children from 2017 and 2018 birth cohorts who interacted with the system and may not account for remaining proportion of zero dose children who were missed.
⇒ Reporting of study estimates is based on the cohort of children registered in the EIR, who can be potentially different than the unregistered children.
⇒ Data on some vaccination events were collected retrospectively which resulted in missing vaccination dates.

INTRODUCTION

Despite improvements in vaccination coverage rates mostly in low-income and middle-income countries (LMICs) in the last decade, an estimated 19.7 million children are never- or under-vaccinated.[1] In the efforts to leave no child behind with immunisation,

there is a growing global interest in reaching the 'zero dose'.[2 3] Due to a lack of consensus on the zero dose definition, the term has often been used to refer to different groups—unvaccinated children,[4] children not immunised for the diphtheria, tetanus, pertussis (DTP)-containing vaccine, pentavalent (DTP, *Haemophilus influenzae* type B and hepatitis B) vaccine, the measles vaccine,[5] the oral polio vaccine and all basic vaccines.[6] Since the coverage of DTP-containing vaccine is an essential milestone used by the immunisation systems globally, the commonly used definition of zero dose children is the infants who have not received any dose of the DTP-containing vaccine by their first birthday. At present, 50% of the 14 million zero dose children (lacking DTP-containing vaccine) in the world are concentrated in six countries: Nigeria, India, the Democratic Republic of the Congo, Pakistan, Ethiopia and the Philippines. Pakistan, with 0.8 million zero dose children (lacking DTP-containing vaccine which is pentavalent vaccine in Pakistan), is the fourth largest contributor to the pool after Nigeria, India and Democratic Republic of the Congo.[7]

While concerted efforts have resulted in improvements in overall immunisation rates in Pakistan, little recent gains have been made in expanding the equitable provision of routine immunisation services by covering zero dose children. There is a lack of understanding regarding the true estimate of zero dose children, who they are, what are their risk factors, where do they live and why does the system consistently misses them. Although zero dose children are often thought to be concentrated in fragile, conflict-affected and displaced settings,[8] the evidence in support of that in Pakistan's context is limited. The official coverage estimates are produced often at the national, provincial or district level[9] and fail to provide granular-level information. The paucity of estimates at a microgeographic level along with inadequate information regarding the characteristics and risk factors of zero dose children poses a huge information gap and limits the system's ability to accurately implement targeted interventions, leaving zero dose children susceptible to vaccine preventable disease (VPDs).

To hold the United Nation's promise of 'Leave No One Behind',[10] it is critically important for the government and other stakeholders to estimate the proportion of zero dose children at a microgeographic level, their sociodemographic characteristics and risk factors. Additionally, it is vital to delineate the geographical locations of zero dose children to identify if they exist in clusters, and if yes, where are these clusters located. Lastly, there is a need to understand why are the zero dose children missed by the health system and what are the most effective strategies to cover them. This critical information is important for immunisation systems to implement targeted approaches for reaching zero dose children, and ensuring their immunisation completion as per the WHO recommended immunisation schedule.

We estimated the proportion of zero dose children among children who interacted with the health system during their first year of life, by district in Sindh, Pakistan and delineated their sociodemographic characteristics and risk factors.

METHODS

Population

As per the population estimates of 2020, Sindh province, in the south of Pakistan has an annual birth cohort of 1.7 million,[11] and is home to 47.9 million[12] people. It has a population density of 339.9 people/km^2[12] and is spread across 6 divisions comprising 29 districts further subdivided into 1123 union councils (UCs; the smallest geographic administrative unit in Pakistan).[13] The median population of UCs is 37 554 (range: 2926–265 842). The urban and rural median population of districts is 403538 (range: 85705–3914757) and 767788 (range: 0–1517590), respectively.[11] The poverty index of the province is 0.28 (district range: 0.02–0.50).[14] The literacy rate for the province is 58% (male=68%; female=47%; urban=73%; rural=39%).[15] The annual target population (0–23 months old children) for Expanded Programme on Immunisation (EPI) was 3.5 million in 2020, the immunisations are administered predominantly through public services (1518 immunisation centres supplemented by outreach), with an additional 225 private clinics.[16] Approximately 60% of all immunisations in the province occur at fixed centres, whereas the rest are delivered through routine and enhanced outreach sessions.[17] Routine outreach is defined as immunisation sessions held in a location other than the immunisation centre, from which vaccinators can go out and return the same day, whereas enhanced outreach is defined as a series of immunisation outreach sessions covering geographic area outside the radius of routine activities. The number of vaccination centres and vaccinators per 1000 population of children under 2 years is 0.98 (range: 0.48–1.84)[13] and 2.07 (range: 1.13–3.02), respectively. The median distance to the nearest immunisation fixed site (calculated from the centre of UC) is 0.17 km (IQR: 0.03–0.63 km) in urban UCs compared with 0.49 km (IQR: 0.04–2.19 km) in rural UCs.

Data source

We used immunisation records from the Government of Sindh's Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry (ZM-EIR). ZM-EIR is an Android-based application for immunisation management that enables vaccinators to enrol 0–23 months old children at their first vaccination administered through the registry and follow-up for subsequent immunisation events.

The ZM-EIR was first deployed in October 2017, and has now been scaled up across all 29 districts of Sindh, where it is used by 2401 vaccinators (including 14.2% females) working at 1518 public and 131 private immunisation clinics. As of 31 December 2020, ZM-EIR enrolled >4.2 million children and >1.4 million women, and recorded >39 million immunisation events. ZM-EIR enrolled 30% and 83% of the EPI estimated annual birth

cohorts of 2017 and 2018 (1 369 832 and 1 417 672, respectively) for the districts where it was operational (Despite the limitation of enrolling only a subset of Sindh's birth cohort, the study creates value in providing useful information on children who are often missed by the system).

Study design and procedures

We analysed child-level longitudinal immunisation records of 0–23 months children enrolled in the ZM-EIR from 2 October 2017 to 31 December 2020, for 27 of the 29 districts of Sindh. District Khairpur and District Dadu were excluded from our analysis, as ZM-EIR was launched in these districts in 2020. We extracted data of children born in 2017 and 2018 on immunisation history including vaccine name, date of vaccine administration, geo-coordinates of vaccine administration site (fixed site, outreach) and child's age at vaccination, child's profile including sex, date and place of birth (home, maternity home, hospital), maternal education, modality of immunisation service delivery at enrolment and follow-up (fixed, outreach, mobile immunisation vans or enhanced outreach), opting for SMS reminder service and geographical location of household (district name, UC name, urban vs rural area and slums) (based on EPI-Sindh's classification of slum areas in seven districts of Karachi and Hyderabad) (source: Civil Society Human and Institutional Development Programme (CHIP) study/profiling of slums in Hyderabad and Karachi). Slum is a contiguous settlement where the inhabitants are characterised as having inadequate housing and basic services. Slum analysis was limited to EPI identified slums in seven districts of Hyderabad and Karachi; slum UCs were defined as having >75% population living in slum areas. A total of 97.5% (233/239) of the total slum UCs in Hyderabad and Karachi were in urban areas, whereas 2.5% (6/239) were in rural areas. Additionally, we calculated the displacement distance (direct distance between two points) between the child's enrolment location and the nearest fixed EPI centre for a subset of children who were enrolled through outreach activities in Division Karachi, Pakistan.

All children who did not receive a pentavalent vaccine during their first year of life were assigned a zero dose status. Zero dose children were further categorised into zero dose covered (vaccinated) children who received pentavalent vaccine between their first and second birthday or after their second birthday, and not covered (not vaccinated) zero dose children who persistently failed to receive the pentavalent vaccine. For all categories, intuitive proxies for missing vaccination dates were used for cases where caregivers of children provided the vaccination data retrospectively at the time of enrolment or follow-up vaccination recorded in the ZM-EIR and did not remember the vaccination dates. We applied logic intuitions based on the recommended age for each vaccination (as per the EPI schedule) to calculate the missing vaccination dates of each child using their non-missing vaccination dates.

Vaccination schedule

Pakistan's routine EPI immunisation schedule includes 6 visits and covers 11 VPDs including tuberculosis (BCG), polio ((oral (OPV) and inactivated polio vaccine (IPV)), DTP, *Haemophilus influenzae* type B and hepatitis B (pentavalent vaccine), pneumococcal diseases (PCV-10), rotavirus diarrhoea (rotavirus), and measles (measles). The first visit is due at child's birth, when the vaccines BCG and OPV-0 are given, the second visit at 6 weeks, when pentavalent-1, PCV-1, rotavirus-1 and OPV-1 are administered, third visit at 10 weeks, when pentavalent-2, PCV-2, rotavirus-2 and OPV-2 are given, fourth visit at 14 weeks, when pentavalent-3, PCV-3, OPV-3 and IPV are given, fifth visit at 9 months, when measles-1 is administered and sixth and the last visit at 15 months when measles-2 is given. Typhoid conjugate vaccine and second dose of IPV have also been added in EPI's fifth visit since 1 January 2020 and 3 May 2021, respectively.

Although, according to the EPI schedule, it is recommended that children complete their immunisation schedule within the age of 0–23 months, vaccinators sometime offer vaccinations to children above 23 months of age as well who connect with the system.

Outcome

The primary outcome was the proportion of zero dose children defined as children who failed to receive any dose of pentavalent vaccine by their first birthday among the 2017 and 2018 birth cohorts enrolled in ZM-EIR in Sindh province. The crude male-to-female (M:F) ratios, the proportion of slum versus non-slum enrolments, missed opportunities for vaccination (MOV) (defined as any contact with health services by a child who is eligible for vaccination, which does not result in the child receiving the vaccine doses for which he or she is eligible), up-to-date coverage at 24 months (calculated as the proportion of 0–24 months children who receive vaccinations by 24 months of age) were compared for zero dose and non-zero dose cohorts. Furthermore, we compared the statistically significant differences in the characteristics of zero and non-zero dose cohorts using the absolute differences (95% CI, p value) for differences in percentage points (pp) and % population proportions. Lastly, the zero dose status was used as an outcome in the multivariate regression analysis.

Statistical analysis

For summary measures, we reported frequencies (%) for categorical data, and median and IQR for continuous data, by child's sex. The percentage of missing entries for each variable including child's place of birth, modality of enrolment event, mother's education, SMS reminder enrolment were reported. We compared coverages across vaccines, geographic variation, distance to the nearest vaccination site and sex by zero dose status. Factors influencing the probability of a child being zero dose were explored through logistic regression analysis using generalised linear modelling. The a priori specified

covariates were selected based on evidence and knowledge, including sex,[18 19] place of birth,[20] enrolment area (urban/rural status), enrolment vaccination site (fixed/outreach/enhanced outreach/mobile)[21] and maternal education.[22 23] We used a forward stepwise approach for final multivariable model selection. We specified p value of 0.05 for entry and 0.10 for removal as the criterion for multivariable model selection to identify a parsimonious model with the lowest Akaike's information criterion score. The list of variables included in the final adjusted model included child's sex, place of birth (hospital, maternity home, home), enrolment area (urban vs rural), enrolment event type (static/fixed, enhanced outreach, mobile immunisation van, routine outreach) and mother's education (in years). All tests were two-sided, and the measure of statistical significance was set at 0.05. We performed statistical analyses with Stata, V.14 (StataCorp, College Station, Texas, USA). Digital maps were used to review the percentage change in immunisation coverage by the district and UC using QGIS (V.3.12).

Patient and public involvement

The parents and caregivers of children or the public were not involved in our research's design, conduct or reporting, or dissemination plans.

RESULTS

Between 2 October 2017 and 31 December 2020, ZM-EIR enrolled 1 467 975 children from the 2017 and 2018 birth cohorts, out of whom 10.6% (population proportion; (95% CI 10.55 to 10.65)) were zero dose (infants who have not received a single dose of pentavalent by their first birthday) (table 1). Out of the total zero dose children, 39.6% (population proportion; (95% CI 39.36 to 39.84)) had received pentavalent-1 by their second birthday. However, 5.6% (population proportion; (95% CI 5.56 to 5.64)) of the total enrolled children remained zero dose by their second birthday. Of these 82 714 persistently zero dose children, 12.9% (population proportion; (95% CI 12.67 to 13.13)) had contact with the EIR through routine or enhanced activities, at least once after becoming due for the pentavalent vaccination (data not shown). Sociodemographic characteristics differed across the two cohorts; notably, zero dose children compared with non-zero dose children had a lower proportion of hospital-based births (28.5% vs 34.0%; difference 5.5 pp; (95% CI 5.26 to 5.74); p<0.001). Additionally, there was a higher prevalence of zero dose among children from slums (49.5% vs 42.3%; difference 7.2 pp; (95% CI 6.93 to 7.46); p<0.001) (table 1). The median vaccination age of zero dose children compared with non-zero dose children was lower at the first visit (0.4 months vs 0.5 months; difference 0.1 months; (95% CI −0.10 to −0.09); p<0.001). Out of the 154 881 zero dose children, 84.2% (population proportion; (95% CI 84.01 to 84.38)) received BCG vaccine, only 46.6% (population proportion; (95% CI 46.35 to 46.85)) ever received the pentavalent vaccine and 23.1% (population proportion; (95% CI 22.89 to 23.31)) completed their vaccination schedule with the second dose of measles vaccine.

A total of 7.6% (110 971/1 467 975) more boys than girls were enrolled in the ZM-EIR (online supplemental file 1 and figure 1). However, the difference between the enrolment rates of boys and girls was higher in the non-zero dose cohort (crude M:F ratio: 1.17, district range: 1.10–1.34) compared with the zero dose cohort (crude ratio: 1.14, district range: 1.03–1.40). In 36.5% (342/937) UCs, there was a higher proportion of girls as compared with boys among the children who received the pentavalent vaccine in the second year of life (data not shown). Moreover, children residing in districts with low Multidimensional Poverty Index had higher zero dose prevalence (online supplemental file 1).

The difference in the up-to-date vaccination coverage at 24 months among non-zero dose and zero dose children was more pronounced in the vaccines administered later as compared with vaccines administered earlier in the schedule (difference 46.0 pp in measles-2 coverage (95% CI 45.84 to 46.16) (53.4% (95% CI 53.31 to 53.49) vs 7.4% (95% CI 7.27 to 7.53), respectively); difference 15.2 pp in BCG coverage (95% CI 14.99 to 15.41) (96.1% (95% CI 96.06 to 96.14) vs 80.9% (95% CI 80.69 to 81.11), respectively) (figure 2).

Among the non-zero dose children, the primary mode of pentavalent vaccination was through fixed site (72.0%). However, among the covered zero dose children in the second year, the predominant vaccination modality for pentavalent was overall outreach (routine outreach=33.0%; enhanced outreach=20.2%) and beyond second birthday was primarily through enhanced outreach (57.8%) (online supplemental file 2). The MOV for pentavalent-1 was higher for zero dose cohort, as compared with the non-zero dose cohort (1.8% vs 0.3%; difference 1.5 pp; (95% CI 1.43 to 1.57); p≤0.001) (online supplemental file 3). The dropout rates were consistently higher among the zero dose cohort as compared with the non-zero dose cohort except the dropout rates between pentavalent-1 to measles-1 and pentavalent-3 to measles-1 (zero dose range: 3.3%–48.3%; non-zero dose range: 7.4%–23.9%) (online supplemental file 4).

Mean displacement distance between the enrolment site and the nearest EPI fixed site of children enrolled through outreach activities in Karachi was higher for zero dose as compared with non-zero dose cohort (1.16 km vs 0.96 km, respectively) (figure 3). Breakdown of the slum and non-slum areas showed a more pronounced mean difference between the two cohorts (zero dose children: 1.11 km in slum and 1.23 km in non-slum vs non-zero dose children: 0.95 km in slum and 0.98 km in non-slum).

Zero dose prevalence varied between and within the 27 districts. District-level prevalence ranged from as low as 3.0% (population proportion (95% CI 2.89 to 3.11)) in District Shaheed Benazir Abad to 17.7% (population proportion; (95% CI 17.23 to 18.17)) in District Jacobabad (online supplemental files 1 and 5). Over half

Table 1 Sociodemographic characteristics of covered zero dose (by second birthday and after second birthday), not covered zero dose, total zero dose and non-zero dose children from 2017 and 2018 birth cohorts enrolled in ZM-EIR in Sindh province, by child's sex (n=1 467 975)

	Zero dose at first birthday (n=154 881)												Non-zero dose children (n=1 313 094)		
	Covered (vaccinated) by second birthday (n=61 345)			Covered (vaccinated) after second birthday (n=10 666)			Not covered (n=82 714)			Total*					
	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male
	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%
Total	61 345 (100)	47.9	52.1	10 666 (100)	46.8	53.2	82 714 (100)	45.8	54.2	154 881 (100)	46.7	53.3	1 313 094 (100)	46.2	53.8
Place of birth															
Home	10 111 (16.5)	15.2	17.6	1604 (15.0)	14.0	15.9	17 975 (21.7)	20.3	22.9	29 708 (19.2)	17.8	20.4	315 373 (24.0)	23.1	24.8
Maternity home	1453 (2.4)	2.3	2.4	244 (2.3)	2.4	2.2	3944 (4.8)	4.8	4.8	5644 (3.6)	3.6	3.7	60 330 (4.6)	4.6	4.6
Hospital	10 691 (17.4)	16.6	18.2	2047 (19.2)	18.8	19.6	31 308 (37.9)	37.2	38.4	44 078 (28.5)	27.5	29.3	445 860 (34.0)	33.5	34.4
Missing	39 090 (63.7)	65.8	61.8	6771 (63.5)	64.8	62.3	29 487 (35.7)	37.7	33.9	75 451 (48.7)	51.0	46.7	491 531 (37.4)	38.9	36.2
Enrolment area															
Rural	48 153 (78.5)	77.9	79.1	9406 (88.2)	87.9	88.4	65 784 (79.5)	79.0	80.0	123 446 (79.7)	79.1	80.2	1 113 986 (84.8)	84.5	85.1
Urban	13 192 (21.5)	22.1	20.9	1260 (11.8)	12.1	11.6	16 930 (20.5)	21.0	20.0	31 435 (20.3)	20.9	19.8	199 108 (15.2)	15.5	14.9
Slums†	11 984 (47.1)	47.1	47.1	1236 (45.7)	45.7	45.8	17 276 (47.4)	47.8	47.1	32 008 (49.5)	49.8	49.2	203 476 (42.3)	42.5	42.0
Non-slums	13 443 (52.9)	52.9	52.9	1466 (54.3)	54.3	54.2	19 143 (52.6)	52.2	52.9	32 645 (50.5)	50.2	50.8	278 024 (57.7)	57.5	58.0
Enrolment event															
Fixed site	33 227 (54.2)	53.6	54.7	5370 (50.3)	49.4	51.2	67 241 (81.3)	80.6	81.9	105 930 (68.4)	67.5	69.2	939 510 (71.5)	70.9	72.1
Routine outreach	17 844 (29.1)	29.1	29.1	2359 (22.1)	23.1	21.2	12 123 (14.7)	15.1	14.3	32 369 (20.9)	21.3	20.5	315 705 (24.0)	24.5	23.7
Enhanced outreach	10 086 (16.4)	17.0	15.9	2882 (27.0)	26.9	27.1	2923 (3.5)	3.7	3.4	15 912 (10.3)	10.7	9.9	57 295 (4.4)	4.6	4.2
Mobile immunisation vans	188 (0.3)	0.3	0.3	55 (0.5)	0.6	0.5	88 (0.1)	0.1	0.1	331 (0.2)	0.2	0.2	193 (0)	0	0
Missing	0 (0)	0	0	0 (0)	0	0	339 (0.4)	0.4	0.4	339 (0.2)	0.2	0.2	391 (0)	0	0
Mother's education (in years)															
0	9957 (16.2)	15.7	16.8	1597 (15.0)	14.8	15.1	17 806 (21.5)	21.2	21.8	29 376 (19.0)	18.5	19.4	282 933 (21.5)	21.3	21.7
1–5	9440 (15.4)	14.0	16.7	1629 (15.3)	14.6	15.9	23 285 (28.1)	26.6	29.4	34 376 (22.2)	20.7	23.5	335 635 (25.6)	24.5	26.5
6–8	1228 (2.0)	1.9	2.1	275 (2.6)	2.5	2.7	4239 (5.1)	5.2	5.1	5746 (3.7)	3.7	3.7	58 641 (4.5)	4.4	4.5
9–10	1103 (1.8)	1.9	1.7	213 (2.0)	1.9	2.1	4463 (5.4)	5.3	5.5	5790 (3.7)	3.7	3.8	83 243 (6.3)	6.3	6.4
11–12	328 (0.5)	0.5	0.6	88 (0.8)	0.8	0.9	1791 (2.2)	2.1	2.2	2208 (1.4)	1.4	1.5	33 736 (2.6)	2.6	2.6
>12	172 (0.3)	0.2	0.3	33 (0.3)	0.3	0.4	944 (1.1)	1.1	1.2	1149 (0.7)	0.7	0.8	21 289 (1.6)	1.7	1.6
Missing	39 117 (63.8)	65.8	61.9	6831 (64.0)	65.3	63.0	30 186 (36.5)	38.5	34.8	76 236 (49.2)	51.5	47.3	497 617 (37.9)	39.3	36.7

Continued

Table 1 Continued

	Zero dose at first birthday (n=154 881)												Non-zero dose children (n=1 313 094)		
	Covered (vaccinated) by second birthday (n=61 345)			Covered (vaccinated) after second birthday (n=10 666)			Not covered (n=82 714)			Total*					
	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male
	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%
Year of birth															
2017	19 009 (31.0)	30.3	31.6	3451 (32.4)	34.3	30.6	9302 (11.3)	11.0	11.4	31 814 (20.5)	20.5	20.6	415 993 (31.7)	31.0	32.3
2018	42 336 (69.0)	69.7	68.4	7215 (67.6)	65.7	69.4	73 412 (88.7)	89.0	88.6	123 067 (79.5)	79.5	79.4	897 101 (68.3)	69.0	67.7
Up-to-date BCG coverage at 12 months	16 775 (27.3)	26.1	28.5	3801 (35.6)	33.8	37.2	73 583 (89.0)	88.6	89.3	94 159 (60.8)	59.3	62.1	80.0	79.9	80.1
Vaccination coverage															
BCG	45 470 (74.1)	73.3	74.8	9848 (92.3)	92.2	92.5	74 932 (90.6)	90.3	90.8	130 360 (84.2)	83.5	84.7	1 270 719 (96.8)	96.7	96.8
Penta-1	61 345 (100.0)	100.0	100.0	10 666 (100.0)	100.0	100.0	–	–	–	72 167 (46.6)	47.7	45.7	1 313 094 (100.0)	100.0	100.0
Penta-2	46 318 (75.5)	75.6	75.4	6786 (63.6)	64.1	63.2	–	–	–	53 267 (34.4)	35.3	33.6	1 215 740 (92.6)	92.6	92.6
Penta-3	36 709 (59.8)	60.1	59.6	6019 (56.4)	57.7	55.3	–	–	–	42 867 (27.7)	28.5	26.9	1 118 867 (85.2)	85.3	85.2
Measles-1	53 390 (87.0)	86.8	87.3	9750 (91.4)	91.1	91.7	6085 (7.4)	7.5	7.2	69 298 (44.7)	45.6	44.0	1 063 316 (81.0)	81.1	80.9
Measles-2	26 745 (43.6)	43.6	43.6	6183 (58.0)	58.9	57.2	2877 (3.5)	3.5	3.4	35 827 (23.1)	23.6	22.7	809 387 (61.6)	61.7	61.6
SMS reminders															
Opted	8263 (13.5)	13.6	13.4	528 (4.9)	5.2	4.7	10 138 (12.3)	12.6	12.0	18 956 (12.2)	12.5	12.0	239 780 (18.3)	18.6	18.0
Not opted	51 732 (84.3)	84.2	84.5	5454 (51.1)	50.2	52.0	69 825 (84.4)	84.0	84.8	127 140 (82.1)	81.7	82.4	965 454 (73.5)	73.1	73.9
Missing	1350 (2.2)	2.2	2.2	4684 (43.9)	44.6	43.3	2751 (3.3)	3.4	3.3	8785 (5.6)	5.8	5.6	107 860 (8.2)	8.3	8.1
Age at vaccination (in months)	**Median (IQR)‡**	**IQR**	**IQR**	**Median (IQR)**	**IQR**	**IQR**	**Median (IQR)**	**IQR**	**IQR**	**Median (IQR)**	**IQR**	**IQR**	**Median (IQR)**	**IQR**	**IQR**
BCG	5.5 (0.3–14.3)	(0.4–14.5)	(0.3–14.2)	0.5 (0.2–1.1)	(0.2–1.2)	(0.2–1.1)	0.3 (0.1–0.7)	(0.1–0.7)	(0.1–0.7)	0.4 (0.1–1.1)	(0.2–1.1)	(0.1–1.1)	0.5 (0.2–1.8)	(0.2–1.9)	(0.2–1.8)
Penta-1	15.3 (13.2–18.2)	(13.2–18.2)	(13.2–18.2)	27.3 (25.4–30.2)	(25.3–30.3)	(25.5–30.2)	–	–	–	15.7 (13.4–19.4)	(13.4–19.3)	(13.4–19.6)	2.0 (1.6–3.1)	(1.6–3.1)	(1.6–3.1)
Penta-2	18.2 (15.3–21.9)	(15.3–21.7)	(15.3–22.2)	28.4 (26.5–31.4)	(26.4–31.4)	(26.5–31.3)	–	–	–	18.3 (15.3–22.6)	(15.3–22.3)	(15.4–22.8)	3.6 (2.9–5.8)	(2.9–5.9)	(2.9–5.8)
Penta-3	20.4 (17.1–24.2)	(17.1–24.1)	(17.2–24.2)	27.8 (25.3–30.7)	(25.4–31.0)	(25.3–30.5)	–	–	–	20.7 (17.3–24.6)	(17.2–24.5)	(17.3–24.7)	5.6 (4.2–9.3)	(4.2–9.3)	(4.2–9.3)
Measles-1	16.2 (13.6–19.3)	(13.6–19.3)	(13.5–19.3)	27.1 (25.0–30.1)	(24.9–30.2)	(25.2–30.1)	22.5 (14.3–24.4)	(14.2–24.4)	(14.7–24.4)	16.8 (13.9–21.3)	(13.9–21.3)	(13.9–21.4)	10.2 (9.4–12.2)	(9.4–12.2)	(9.4–12.2)
Measles-2	25.1 (21.4–29.1)	(21.3–28.9)	(21.4–29.2)	26.4 (24.4–29.5)	(24.4–29.6)	(24.4–29.4)	24.5 (24.4–28.2)	(24.4–27.9)	(24.4–28.4)	25.4 (22.8–29.1)	(22.8–29.0)	(22.9–29.2)	17.4 (15.7–21.4)	(15.7–21.4)	(15.7–21.4)

Continued

Table 1 Continued

	Zero dose at first birthday (n=154 881)										Non-zero dose children (n=1 313 094)		
	Covered (vaccinated) by second birthday (n=61 345)			Covered (vaccinated) after second birthday (n=10 666)			Not covered (n=82 714)			Total*			
	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male
	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%	N (%)	%	%
IPV	17.4 (14.8–21.2)	(14.9–21.2)	(14.8–21.1)	26.7 (24.9–29.2)	(24.8–28.9)	(25.0–29.4)	20.3 (13.6–24.4)	(12.9–24.4)	14.6–24.4)	18.0 (15.1–22.4)	(15.1–22.4)	(15.1–22.5)	5.4 (4.1–8.9)	(4.1–8.9)	(4.1–8.9)

*Coverage status of 0.1% (156/154 881) zero dose children could not be determined due to missing vaccination dates.
†Slum analysis was limited to EPI identified slums in seven districts of Hyderabad and Karachi: slum union councils were defined as having >75% population living in slum areas; 97.5% (233/239) of the total slum UCs were in urban areas, whereas 2.5% (6/239) were in rural areas.
‡IQR (25%–75%).
EPI, Expanded Programme on Immunisation; IPV, inactivated polio vaccine; Penta, pentavalent; UCs, union councils; ZM-EIR, Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry.

of all districts (63.0%; population proportion; (95% CI 44.74 to 81.18)) had >10% zero dose children among those enrolled in the EIR at some point. At a UC level, zero dose prevalence ranged between 0% and 90%, with >10% recorded in 44.7% (population proportion; (95% CI 41.56 to 47.84)) of UCs (data not shown). Micro-geographic analysis showed several clusters of zero dose children across districts, with 34.2% (population proportion; (95% CI 30.70 to 37.70)) clusters having >100 zero dose children in a 5 km radius (online supplemental file 6).

We included 60.3% (884 889/1 467 975) children with complete data for all variables in the regression analysis (table 2). Children enrolled from urban areas (relative risk (RR): 1.20; p<0.001; 95% CI 1.18 to 1.22) were more likely to be zero dose than rural areas. Children with educated mothers (RR: 0.47–0.96; p<0.001; 95% CI 0.45 to 0.98) were less likely to be zero dose compared with children with uneducated mothers. Girls had 2% reduced risk of being zero dose compared with boys. Although, the difference was small, it was marginally significant (RR: 0.98; p=0.015; 95% CI 0.97 to 1.00).

DISCUSSION

One out of 10 children enrolled in the EIR, who had therefore interacted with the immunisation system at birth or later in life were zero dose in Sindh province. The health system failed to leverage the opportunities that it had for interacting with the zero dose children to provide them with a full vaccination package. One out of eight zero dose children received at least one vaccination through routine or enhanced activities, after becoming due for the pentavalent vaccination but failed to receive pentavalent. Additionally, almost 80% zero dose children failed to complete their vaccination schedule. This demonstrates that enrolling children in an EIR system is insufficient to ensure they complete their vaccination schedule. It also highlights the chronic vulnerability of zero dose children to consistently miss vaccines despite establishing contact with the system.[6] Our finding simultaneously suggests moving children out of the zero dose state is particularly critical and underscores the need for intensified supply- and demand-side interventions. The former includes systematic outreach and supplementary immunisation activities, targeting hotspots and missed clusters at frequent and regular intervals to deliver immunisation services while the latter includes creating immunisation-related awareness among caregivers and addressing vaccine hesitancy which might be one of the core reasons for zero dose prevalence despite high proportion of registeration in the immunization system through BCG vaccination coverage.

We found a higher crude M:F ratio among non-zero dose children compared with zero dose children, indicating a comparatively higher female-based sex disparity among the non-zero dose cohorts. However, in our analysis, we found male sex to be an independant predictor

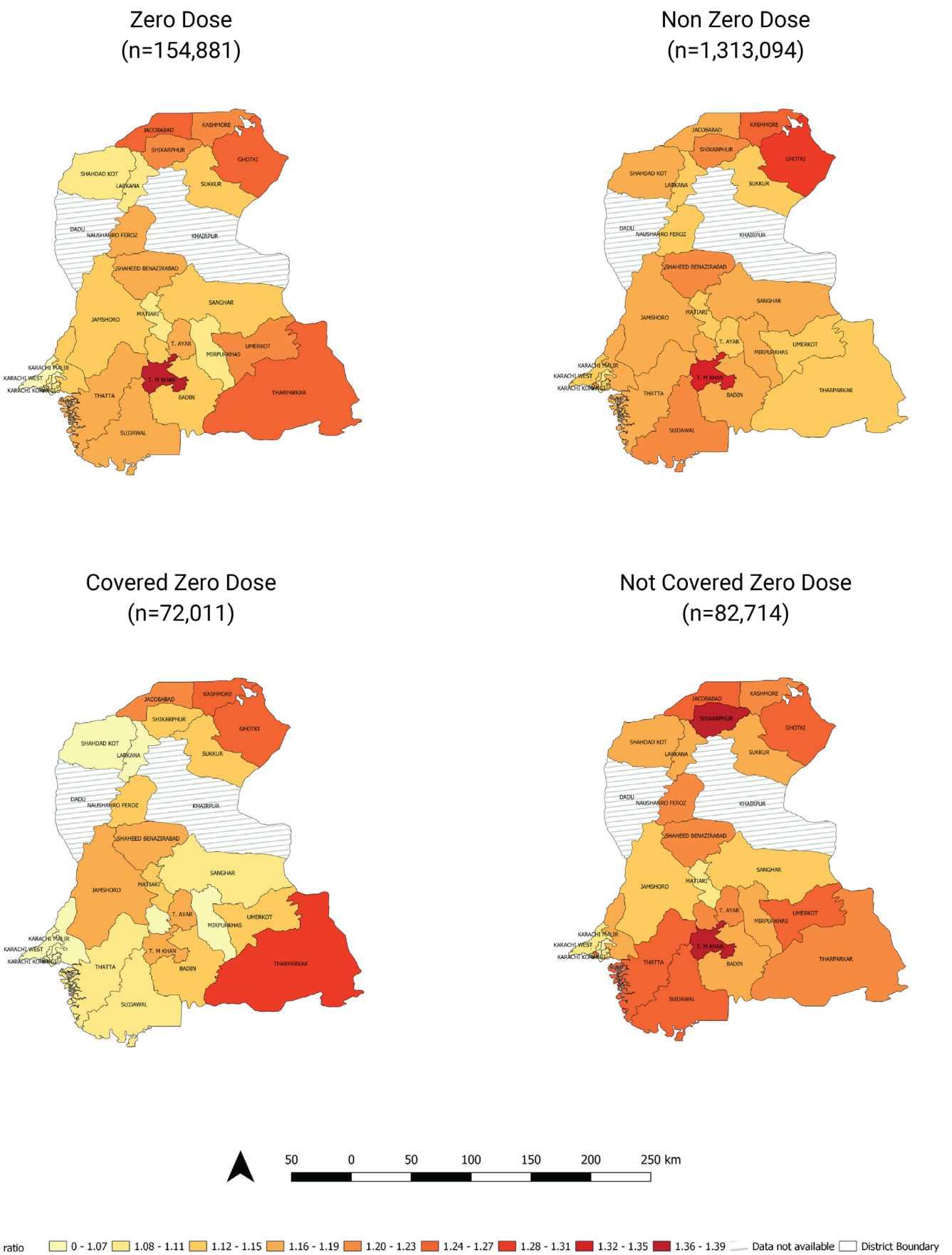


Figure 1 Crude male-to-female (M:F) ratio among zero dose, non-zero dose, covered zero dose and not covered zero dose children from 2017 and 2018 birth cohorts enrolled in Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry in Sindh province, by district (n=1 467 975).

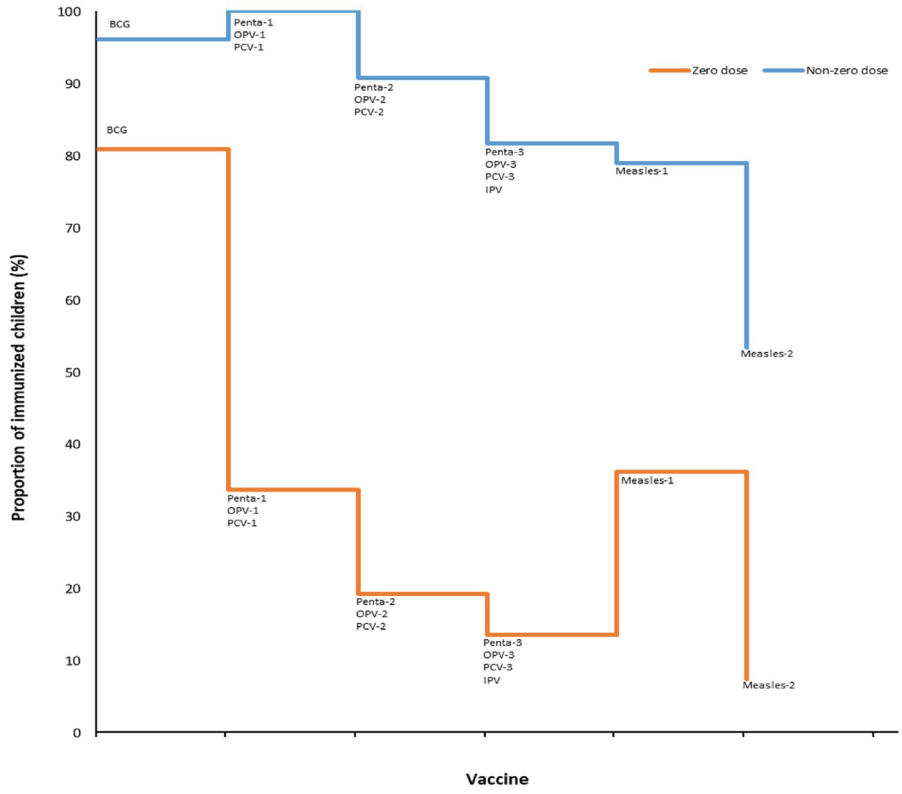
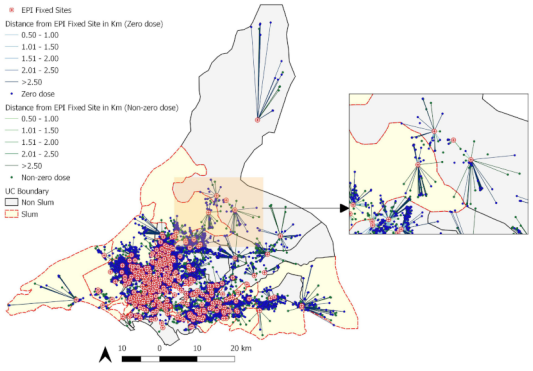


Figure 2 Up-to-date vaccination coverage at 24 months among zero dose and non-zero dose children from 2017 and 2018 birth cohorts enrolled in Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry in Sindh province (n=1 467 975). IPV, inactivated polio vaccine; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine; Penta, pentavalent.

Karachi
(n=33,682)

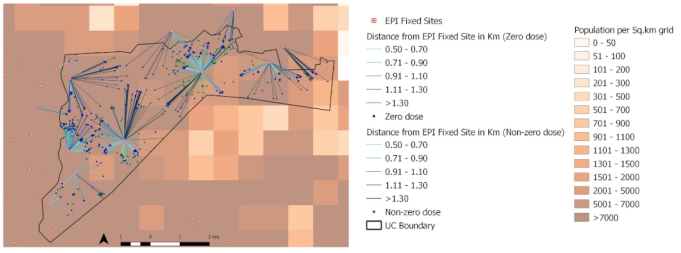


Geo-coordinates falling inside the buffer of 500 meters from the fixed sites were dropped.

Area	Zero dose			Non Zero-dose		
		Distance in Km			Distance in Km	
	# of children	Mean	Standard deviation	# of children	Mean	Standard deviation
Non Slum	3,620	1.23	1.73	11,700	0.98	0.93
Slum	5,042	1.11	0.98	13,320	0.95	0.67
Total	8,662	1.16	1.35	25,020	0.96	0.80

Area	Zero dose			Non Zero-dose		
		Distance in Km			Distance in Km	
	# of children	Median	IQR*	# of children	Median	IQR*
Non Slum	3,620	0.83	0.55	11,700	0.77	0.34
Slum	5,042	0.82	0.57	13,320	0.75	0.52
Total	8,662	0.82	0.56	25,020	0.76	0.42

UC-Gujro, Karachi
(n=1,640)



Geo-coordinates falling inside the buffer of 500 meters from the fixed sites were dropped.

Category	# of children	Distance in Km	
		Mean	Standard deviation
Zero dose	576	1.02	0.35
Non-zero dose	1,064	0.99	0.34

Category	# of children	Distance in Km	
		Median	IQR*
Zero dose	576	0.99	0.50
Non-zero dose	1,064	0.98	0.47

*Difference between 75th and 25th percentile
Population source: Landscan population, 2017

Figure 3 Enrolment locations of zero dose and non-zero dose children from 2017 and 2018 birth cohorts enrolled in Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry through routine and enhanced outreach and their displacement distance to the nearest Expanded Programme on Immunisation fixed sites (in km) in Karachi and Union Council Gujjro, Karachi.

Table 2 Predictors of zero dose status among children from 2017 and 2018 birth cohorts enrolled in ZM-EIR in Sindh province (n=884 889)

	Unadjusted analysis				Adjusted analysis			
Predictor	Risk ratio	P value	95% CI		Risk ratio	P value	95% CI	
Sex								
Female	0.98	0.004	0.97	0.99	0.98	0.015	0.97	1.00
Male	1				1			
Place of birth								
Hospital	1.05	<0.001	1.04	1.07	1.11	<0.001	1.10	1.13
Maternity home	1.00	0.879	0.97	1.03	1.05	0.001	1.02	1.08
Home	1				1			
Enrolment area								
Urban	1.17	<0.001	1.15	1.19	1.20	<0.001	1.18	1.22
Rural	1				1			
Enrolment event type								
Static/Fixed	1.45	<0.001	1.42	1.47	1.51	<0.001	1.48	1.53
Enhanced outreach	2.16	<0.001	2.07	2.25	2.11	<0.001	2.02	2.20
Mobile immunisation van	9.25	<0.001	6.46	13.2	7.63	<0.001	5.35	10.88
Routine outreach	1				1			
Mother's education (in years)								
Primary (1–5)	0.99	0.059	0.97	1.00	0.96	<0.001	0.95	0.98
Secondary (6–8)	0.95	<0.001	0.92	0.98	0.86	<0.001	0.83	0.88
Matric (9–10)	0.69	<0.001	0.67	0.71	0.61	<0.001	0.59	0.63
Inter (11–12)	0.65	<0.001	0.63	0.68	0.57	<0.001	0.55	0.60
Bachelors (>12)	0.54	<0.001	0.51	0.58	0.47	<0.001	0.45	0.50
Uneducated (0)	1				1			

39.7% (583 086/146 797 5) observations were dropped due to missing observations for place of birth, maternal education and enrolment event type.
ZM-EIR, Zindagi Mehfooz (Safe Life) Electronic Immunisation Registry.

of zero dose status. This is in contrast with prior literature from Bangladesh and other LMICs, which has repeatedly identified female-based sex inequities in access to health services, favouring boys and therefore contributing to the marginalisation of women from a young age.[24] A possible explanation for this could stem from the fact that in the Pakistani context, caregivers in patriarchal communities favour taking boys to the vaccination centres when facing logistical and financial challenges, as evidenced by the gender disparity at enrolment. However, girls catch up with their scheduled vaccinations due to extensive outreach vaccination services offered within the communities. Hence, female-based sex discrimination is observed at enrolments which mostly happens through fixed centres, while male-based sex discrimination is evident in pentavalent vaccination.

In Karachi and Hyderabad (the two largest cities of the province), which have a population of 16 416 894 and 2 321 012, respectively, half of the zero dose children reside in slums (97.5% being urban slums). In line with prior literature, we observed an increased risk of being zero dose for children living in urban areas.[25] Our finding may be indicative of the 'urban paradox',[26] although urban settings generally have better access to health services, many children face more severe deprivations than their rural counterparts due to deep inequity and exclusion of marginalised communities. Additionally, there is a higher tendency for children living in urban areas to relocate frequently which results in missed/delayed vaccinations.[27] Moreover, the government undertakes sustained efforts including intensified supplementary immunisation activities and extended periods of enhanced outreach in rural areas.[28]

Several geographic disparities exist among the zero dose cohorts at a district level. Our analysis demonstrates that children are more likely to be zero dose if living further from an EPI centre, compared with their non-zero dose counterparts. An added nuance of this finding is that zero dose children are typically vaccinated with non-pentavalent antigens at an earlier age than their non-zero dose counterparts, despite an assumption that a lower age at BCG would be associated with better immunisation outcomes in subsequent months. Although seemingly counterintuitive, this finding ties in with the

higher mean distance from the EPI centre, as zero dose children are more likely to be enrolled in the EIR through outreach activities, which may reach them at an earlier age than children who are taken to EPI centres by their caregivers. In addition, the early age of first vaccination among the zero dose cohort as compared with the non-zero dose cohort suggests that many zero dose children in Sindh might be missing vaccines due to logistical and access barriers.[29] This finding has extremely important policy implications, as the reversal of trend in the vaccination age for antigens administered later in the schedule suggests a dire need to actively and repeatedly follow-up children enrolled during outreach, from the first contact to immunisation completion.

We found that 1 out of 10 children enrolled in the ZM-EIR did not receive any dose of pentavalent by their first birthday and hence were categorised as zero dose. However, estimates from our study are underestimated. Our findings are based on analysis of observational routine admin data and therefore, differ from the pentavalent-1 vaccination figures reported in the national surveys. For instance, Pakistan Demographic Health Survey estimates the proportion of 12–23 months children who have not received pentavalent vaccine in Sindh to be almost twice more than what we have seen through EIR cohorts (19.4% vs 10.6%).[9] The possible explanation for this is the inclusion of the unregistered/never enrolled cohort of children in the sampling frame of Demographic Health Survey, who are likely to have comparatively poor immunisation outcomes. Nevertheless, the zero dose prevalence among those who are enrolled in the EIR in Sindh is higher than demographically similar LMIC settings, including Bangladesh (1.6%)[30] and Sri Lanka (1.4%),[31] and comparable to global average (15%).[7]

The limitations of our study include reporting of estimates which are based on the data of children registered in ZM-EIR. Therefore, even though our analysis extensively covers the predictors of zero dose children, limited inference can be drawn regarding never-immunised children (never connected with the system), who could potentially be different than the registered children. Another limitation is that although ZM-EIR is currently deployed in all the public immunisation clinics across the entire province, it is gradually expanding to private clinics, and as such, the vaccinations administered through some private clinics were not captured in the EIR. However, it is plausible that children who receive vaccinations through private clinics may be less likely to miss/delay vaccinations since they mostly belong to upper wealth quintiles, and have lower vaccine hesitancy due to improved caregiver awareness. Another limitation is that some data about vaccination events were collected retrospectively, which might have resulted in missing vaccination dates, as caregivers may not remember the exact date of vaccination. Although intuitive proxies were used for missing vaccination dates, unavailability of the actual dates may have biased the results, particularly regarding timeliness of vaccination. Furthermore, in the multivariate analysis, 40% of records were incomplete, with missing information on one or more variables and were therefore dropped, restricting our ability to conduct a robust analysis. Another limitation pertains to the vaccination accessibility analysis. Due to the unavailability of road distances, displacement distances between the enrolment locations and the EPI sites have been used. Nevertheless, the large granular data collected by the EIR have enabled us to analyse inequity in zero dose prevalence at a micro-geographic level, providing key insights into the zero dose landscape of Pakistan.

Out of the total children who interacted with the health system in their first year of life, approximately 10% remained zero dose. Leveraging real-time data to track zero dose children and follow-up with them till the point of immunisation completion is a key strategy that should be adopted by the immunisation programmes. To ensure no child is left behind, there is a further need to conduct an investigation regarding the never-immunised children who are not connected with the system and develop and implement strategies to reach them.

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Contributors SC designed the study. SC, MM, MS, VKD, DAS and MAS have contributed to the implementation of the electronic immunisation registry. SC and HS advised on data analysis. MM and SI extracted the data and did all statistical analyses. SC, MM and HS interpreted the data. SC, MM and HS wrote the paper. MS supported spatial analyses with input from SC and HS. DAS, RS, AKB, MAS and ES reviewed drafts and provided input. MM and SC revised the manuscript drafts. SC, DAS, MM, SI, MS, VKD and MAS had full access to all study data. All authors have given approval of this manuscript to be published and take responsibility for its content.

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