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Poliovirus immunity among children under five years-old in accessible areas of Afghanistan, 2013

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Abstract

Background: Afghanistan remains among the three countries with endemic wild poliovirus transmission, and high population immunity levels are required to interrupt transmission and prevent outbreaks. Surveillance and vaccination of children in Afghanistan have been challenging due to security issues limiting accessibility in certain areas.

Methods: A serosurvey was conducted in 2013 within accessible enumeration areas (EAs) among children aged <5 years using samples collected for a national micronutrient assessment survey to assess poliovirus immunity in Afghanistan. Of 21194 total EAs in Afghanistan, 107 were inaccessible and therefore were excluded from the sampling frame.

Results: Population immunity was high overall but varied for the poliovirus serotypes, and was lowest for type 3 (95% [95% CI: 93%, 96%]) compared to type 1 (99% [95% CI:97%, 99%]) and type 2 (98% [95% CI:96%, 99%]). The proportion of the population immune to all three types was 93% (95% CI: 91%, 95%), and the proportion seronegative for all three types was 0.5% (95% CI: 0.2%, 1.7%).

Conclusion: Except for regional differences in immunity to type 3 virus, there were no other apparent differences in seroprevalence by region or by any of the demographic or nutritional characteristics assessed in this study. The study was not powered to provide provincial level seroprevalence estimates, but Paktika Province, in the South region, had the largest proportion of seronegative specimens for type 1(4 seronegative of 17 serum specimens compared to 14 seronegative of 673 for the remainder of the areas). Among accessible children in Afghanistan, seroprevalence of antibodies to poliovirus was high, with most seroprevalence reported at 95% or

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Conflicts of interest

All co-authors report no potential conflicts of interest.

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greater. Despite high seroprevalence in areas assessed in this study, the continued detection of poliovirus cases in the South and East regions indicate that overall regional vaccination coverage and performance is not sufficient to stop polio transmission.

Summary

Afghanistan, one of three remaining countries endemic for wild poliovirus, aggressively vaccinates children to eradicate polio. Serum polio immunity profiles of Afghan children in accessible areas were overall high to the three wild poliovirus strains.

Keywords

Afghanistan; Poliovirus; Serosurvey; Eradication; Immunity

1. Introduction

Afghanistan is one of the remaining three countries endemic for wild poliovirus (WPV) [1]. Despite significant progress in reducing the number of polio cases from 2013 to date, there is evidence of ongoing circulation in the South region and an increasing number of polio cases in the East region caused by circulation following importations from Pakistan during the second half of 2014 to 2017 [2–4]. This continued transmission jeopardizes the polio eradication efforts in Afghanistan [1,5,6], and high population immunity levels are required to interrupt transmission and prevent outbreaks if importations occur.

Afghanistan administrative routine immunization (RI) coverage data and vaccination coverage surveys provide crude estimates of population immunity; however, these are not direct measures of immunity and are unable to provide information on the true protective immunity profile. Assessment of antibodies to poliovirus through serosurveys provides a direct estimate of population immunity because seroprevalence reflects the effect of vaccination coverage, field vaccine effectiveness, natural infection, and secondary transmission of oral poliovirus vaccine (OPV). This information helps guide program planning to interrupt poliovirus transmission.

During May-September 2013, the Afghanistan Ministry of Public Health (MoPH) in collaboration with Agha Khan University (AKU) conducted a national nutrition survey among women and children in Afghanistan [7]. Fourteen cases of wild poliovirus type 1 were reported in the country in 2013. Trivalent OPV (tOPV), containing poliovirus strains 1,2 and 3, was given as part of RIs at birth, 6, 10, 14 weeks and 9 months. During multiple supplemental immunization activities (SlAs) bivalent OPV (bOPV), covering poliovirus strains 1 and 3, or tOPV were offered to all children under 5 years of age in Afghanistan during 2013 [5]. Because OPV is the cornerstone of efforts to interrupt transmission of poliovirus in Afghanistan, study subjects could have received up to four Rl doses and a variable number of SlA doses depending on age of the child and completeness of coverage during SlAs. Despite years of aggressive vaccination efforts, the country has been challenged by insecurity leaving many areas inaccessible. Furthermore, due to these security challenges, nationwide poliovirus immunity status has not been assessed in Afghanistan and is therefore largely unknown. Serum collected for the 2013 nutrition survey from accessible

regions of the country posed an opportunity to assess the serology status of individuals from accessible areas (Fig. 1). In this study, we determined the serology status of children under 5 years of age from accessible regions of Afghanistan. Anthropometric data and medical history were also assessed to determine if these factors could affect a child's ability to mount an immune response to OPV.

2. Methods

2.1. Population and study design

We acquired approval from the MoPH in early 2015 to use existing specimens collected during a 2013 nutrition survey to estimate population immunity to poliovirus in Afghanistan by assessment of neutralizing antibody seroprevalence among children under 5 years of age. A stratified two-stage sample design was adopted for the nutrition survey [7] with 30 primary sampling units (PSUs) selected from each of 34 provinces in Afghanistan by probability proportional to size (PPS). In total there were 21,194 enumeration areas (EAs)/PSUs (3648 urban and 17,546 rural enumeration areas). Of those, 107 EAs were excluded from the sampling frame due to security concerns (Fig. 1). Thirty primary sampling units (PSUs) were selected from each of 34 provinces in Afghanistan with probability proportional to size (PPS). Blood draws for micronutrient assessments were completed in a subsample of the larger survey and sample size was calculate to provide national estimates. Accordingly, Eighty PSUs/clusters were selected from a total of 1020 PSUs. The clusters were distributed among provinces using PPS. Eighteen households were selected from each PSU. Whole blood samples were collected from all children 6–59 months of age in each participating household of the sub-sampled clusters.

2.2. Demographic and medical history data

Gender, age, maternal education, settlement location and history of recurrent diarrhea were collected using questionnaires. Hemoglobin (Hb) level (anemia indicated by Hb<11g/dL) was assessed from participants' serum.

2.3. Anthropometric assessment

Nutritional status was determined using anthropometric indices and hemoglobin (Hb) levels. Anthropometric indices were calculated using a combination of height, weight and age, and these were compared to the standard distribution of the National Center for Health Statistics/World Health Organization reference population [8]. Categories of malnutrition were based on standard deviation (SD) units (z-scores) below the median of the reference population. Categories were defined as adequately nourished (≥−2 SD), and malnourished (<−2 SD). Low-height-for-age (<−2 SD) indicated stunting, a measure of chronic malnutrition, and low weight-for-height (<−2 SD) indicated wasting, a measure of acute malnutrition. Low weight-for-age (<−2 SD) was a measure of both stunting and wasting.

2.4. Antibody assay

Serum samples were stored at −80 °C in the Nutrition Research Laboratory at the AKU until they were shipped to the Centers for Disease Control and Prevention (CDC) Atlanta Laboratories under an agreement with the MoPH. Neutralization antibody titers against

polioviruses 1, 2, and 3 were measured using standard neutralization assays [9]. Specimens were considered seropositive when titers of poliovirus neutralizing antibodies were ≥ 3 Log2.

2.5. Statistical analysis

Thirty percent (291/981) of children enrolled in the survey did not have a serum specimen available for testing. Chi-square tests were used to compare characteristics of children with specimens (participants) and those without specimens (non-participants). To take advantage of the information on the child and family characteristics that were available for many, but not all, of the children, we used multiple imputation methods to construct 30 complete datasets. Detailed information on the imputation model can be found in the supplementary appendix. Briefly, we used the Ml package [10] in R (3.3.3) to impute missing values on the three types of Sabin titers using mother's education, weight and height of child, hemoglobin level and history of diarrhea in the last two weeks. The proportion seropositive and the variance were estimated for each of the 30 imputed datasets using the survey package [11] in R (3.3.3) accounting for the stratified cluster design, and survey weights for each child. Estimates were combined using Rubin's formulas to obtain proportion seropositive and corresponding 95% logit confidence intervals. The median and interquartile range of polio titers were obtained by calculating the mean of the 30 estimates of the median, 25th, and 75th percentiles that were calculated using the quantile function in the survey package. Description of missing data patterns are presented in Supplementary Figs. 1–3c and Supplementary Tables 1–3. Summary of imputation model inputs are listed in Supplementary Table 4. Multiple imputation diagnostics are presented in Supplementary Figure 4 and Supplementary Table 5.

3. Results

3.1. Description of sample (prior to imputation)

Nine hundred eighty-one children 6–59 months of age were enrolled in the survey. There were 690 serum samples (70% of the original sample) available for testing by the polio assay. Serum was not collected, missing or specimen was of quality that could not be tested for 291 children (to be referred to as nonparticipants) that originated from 70 of the 80 selected PSUs in 24 of the 25 strata. Unweighted counts and percents of demographic and other characteristics of the study sample are included in Table 1. Among children in the sample, 44% were 1–3 years of age and 48% were female; 43% of their mothers were illiterate. Recurrent diarrhea was reported for 37% of children, 6% were classified as having wasting/acute malnutrition, 38% were stunted/chronically malnourished, and 20% were underweight. There was a considerable amount of missing data on hemoglobin (7%), stunting (13%), wasting (12%), history of diarrhea (42%) and education (43%).

Participants and non-participants were significantly different in the prevalence of recurrent diarrhea and anemia which were reported more frequently among non-participants (p =

Appendix A. Supplementary material
Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.008.

0.009 and $p < 0.0001$ respectively). In addition, the proportion of nonparticipants varied by region (Table 1, Fig. 2).

3.2. Population immunity (prior to imputation)

For type 1, there were 18 negative specimens from 13 different clusters. For type 1, one cluster in Paktika (in the South East region) had 4 negative specimens of 17 total specimens available, compared to 14 seronegative of 673 for the remainder of the areas. For type 2, there were 22 negative specimens from 16 clusters and the Paktika cluster had 5 of the negative specimens. For type 3, there were 60 negative specimens from 34 clusters; 9 were from the Paktika cluster.

3.3. Population immunity (imputed)

Median poliovirus antibody titers in the population were high overall but varied for the poliovirus types, being lowest for type 3 compared to types 1 and 2 (Table 2). The proportion of the study population immune to all three types was 93% (95% CI: 91%, 95%), and 0.5% (95% CI: 0.2%, 1.7%) were seronegative for all three types. Observed immunity levels to the 3 poliovirus types were similar among the regions, though the sample sizes were too small to test for differences (Table 3, Fig. 2).

Antibody seroprevalence by demographic and nutritional characteristics for the three poliovirus types are shown in Table 4. No apparent differences are seen by gender, age, hemoglobin level, diarrhea, weight-height, height-age and weight-age.

4. Discussion

To our knowledge, this was the first national study of the immune status against polioviruses among children in Afghanistan that stratified by region. Results from this study give a glimpse of the country's immunity status during the 1–6 months preceeding the survey and determine if vaccination efforts are reaching their targets. This study differs from two prior Afghanistan vaccine coverage and serosurvey studies. One study conducted a retrospective analysis of population vaccination coverage and immunity among Afghan children during 2001–2011 [12]; however, though details of the southern region of Afghansitan were described, the other regions were cumulatively depicted as "other areas" so rather than having region-specific details, the details were grouped under a single geographic area. The second study was a cross-sectional study describing polio neutralizing antibody levels in children at a health facility located in Kandahar Province in the southern region [13]. Their findings indicated that overall children from Kandahar had antibody titers higher than children from elsewhere, but this study was limited in scope because results were based on the patient population collected from a single facility. Our study shows immunity details of each region of the country that has not been described previously.

Overall, findings in this study show that titers and seropositivity in Afghanistan were higher for types 1 and 2 compared to type 3, a finding supported by similar poliovirus antibody seroprevalence studies conducted in Pakistan, Nigeria and the United States [14–16]. However, these results need to be interpreted with caution for several reasons. One concern is that this study relied on data from 2013 and could potentially be considered outdated.

Significant regional insecurity has been a longstanding challenge in conducting studies in Afghanistan. Utilizing serum collected from a 2013 nutrition survey was a novel opportunity to acquire a first “snapshot” of the polio serology status among children under 5 years of age among select areas of the country. The benefits of this 2013 study are two-fold: (1) it is a starting point to track regional polio serology trends, and (2) data collected from 2013 are pertinent because polio case numbers, positive environmental samples and overall performance indicators in Afghanistan have not changed significantly and in some instances gotten worse during 2013–2018 [17–20].

Another limitation was that 107 EAs with security concerns, therefore considered inaccessible, were excluded from the sampling frame. Asssessing children among only accessible areas in Afghanistan where RI and SlAs are more readily offered to children, can significantly bias seroprevalence estimates upwards. This limitation is not addressed with the imputation methods used here. The imputation approach attempted to handle the missing data on children who were enrolled but for which no serum specimen was available. The imputation model may also have limitations as some of the characteristics we used to inform the imputation of the titers were missing, and thus imputed in the process. ln addition, we were limited by available and accurate data on characteristics of study subjects and might lack information on other informative characteristics associated with seroprevalence. The poliovirus antibody assay is also not capable of differentiating between antibodies resulting from immunization versus an infection by exposure to circulating vaccine virus or wild virus. This study helped us gain a general understanding of vaccination effectiveness and coverage in accessible areas. Malnutrition and co-morbid conditions (diarrhea and anemia) are common conditions among Afghan children. The findings of this study suggest that these health factors do not negatively affect vaccine effectiveness. Finally, despite the vaccine switch to bOPV [14] and no reports of WPV2 cases globally, understanding the immunity status against type 2 is important since circulating vaccine derived poliovirus is a potential but real concern [21–24]. Though our 2013 serosurvey showed high titers against type 2, a recent serosurvey conducted in Khandahar showed decreased seroprevalence against polivirus type 2 as a result of the vaccine switch in 2016 [13]. Children in this endemic country may not be currently protected against type 2 poliovirus.

Biases created by inaccessibility and non-response are not unique to this serosurvey. In serosurveys where we have conducted primary data collection we imploy a number of methods to overcome these challenges including: (1) social mobilization prior to implementation of field data collection to ensure that communities are aware that teams will be coming from the Ministry to assess the health of their children; (2) adding other health assessments, such as micronutrients assessments, and communicating the results to the parents as an incentive for participation in the survey; and (3) collecting information on households that refuse to participate in the surveys in order to estimate the possible effects of non-response on the results and when appropriate the data is used to conduct sensitivity analyses. Engaging communities, respecting local cultural practices and understanding community needs are essential in reaching populations in certain areas of Afghansistan.

These findings corroborate the surveillance data that shows missed onging circulation in the South and East Regions despite many areas being accessible (Fig. 1). In 2013, 13 of the 14

WPV1 cases occurred in Kabul and the East region and three circulating vaccine derived poliovirus type 1 cases occurred in the South region, mostly among districts accessed in this study. Furthermore, during 2013–2015, 26 of 62 WPV1 cases (58%) occurred in the South and East regions. Paktika province, in the South region, is a particular area of concern because of the high number of seronegative samples; the first WPV1 case occurred in August 2014 and since that time, nine WPV1 cases have been detected in that province with the latest confirmed on December 2016. Furthermore, between January 2013-August 2014, six cases of polio orphan viruses (i.e. genetic divergence ≥1.5% from the nearest match [25]) were confirmed in Kabul, South and East regions indicating virus circulation occurred undetected for approximately 1.5– 2years [3]. The cases (WPV1 or orphan) did not trigger an effective escalation in programmatic response because cases continued to occur in the regions. Rather, despite our serosurvey of accessible areas showing good vaccination coverage, the regional scenario paints a picture of poor vaccine coverage through poor vaccination campaign performance, poor case response vaccinations and/or resistance of caregivers to accept polio vaccines [26]. These problems are compounded by operational, technical and public- perception challenges such as oversight and ownership of polio activities, coordination between partners, effective usage of field data to improve SIAs, community frustration of “polio-only focus” without addressing other public health needs (e.g. nutrition, clean water) and countering misinformation that have negative effects on the polio eradication program [20]. This underscores the importance of utilizing multiple sources of data - epidemiology, serology, monitoring and evaluations, field reports, and community surveys - on all areas (accessible and inaccessible) among regions to drive effective and targeted programmatic response. No single data source is without its weakness so a serosurvey serves as an additional supplemental piece of information that can be used to complement other sources to gain a better perspective of the quality of the country’s polio eradication activities.

These findings suggest that attention should be given to a targeted serosurvey in the transmission zone and the high risk areas particularly in areas that are often inaccessible. This could be a worthwhile effort that can inform implementation of the national immunization program in Afghanistan. Most importantly, our goal is to use targeted serosurvey data as a complement to other sources of data, as opposed to a sole source, to identify gaps in surveillance, case response and immunization to guide eradication efforts that help Afghanistan reach polio-free status. Consequently, we are in the process of conducting a serosurvey in Afghanistan focusing on tertiary pediatric health centers in different regions of the country, regardless of security status of their residence which will supplement the serosurvey findings presented in this study, and will provide a more encompassing picture of the country’s immunity profile against polio.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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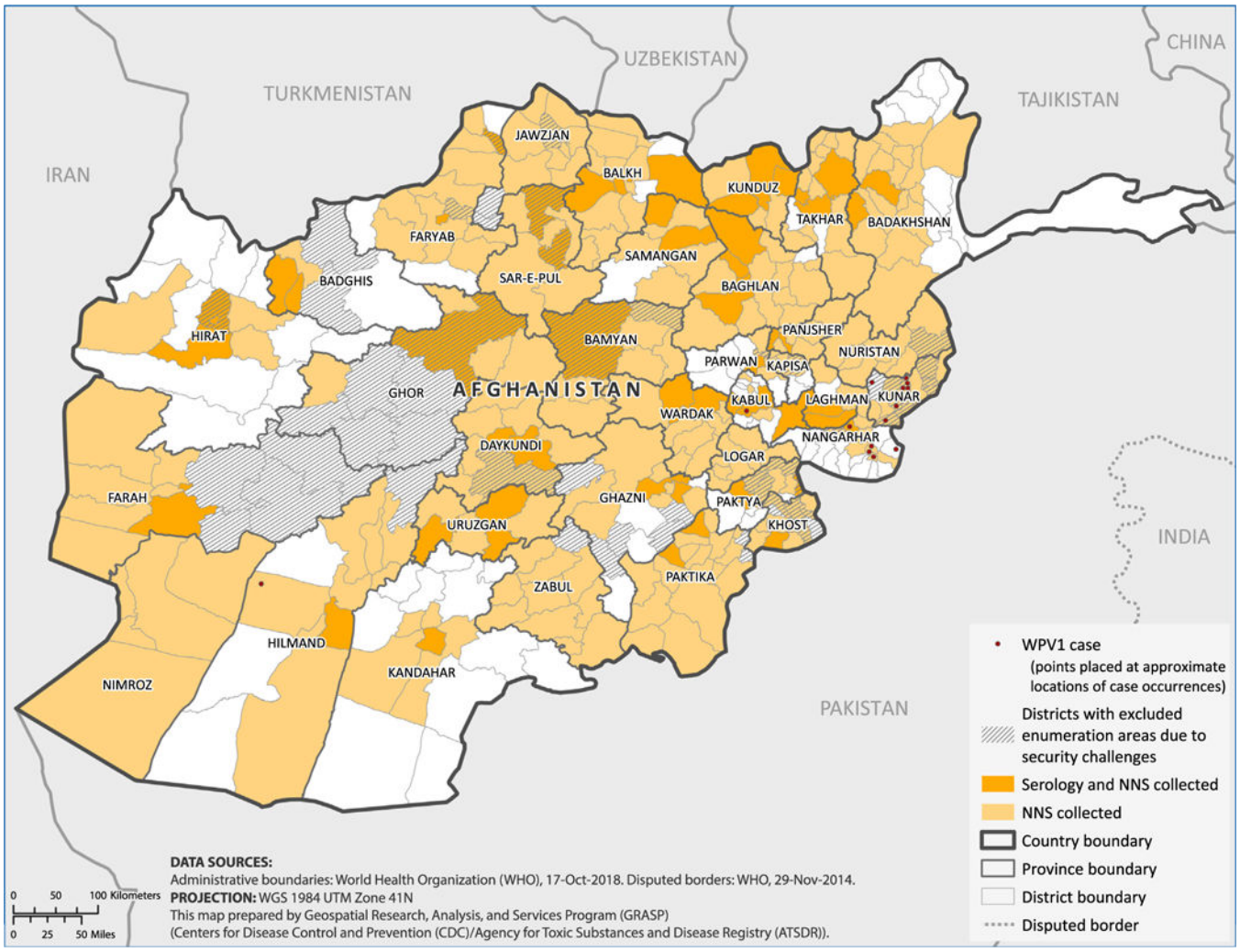

Fig. 1.

Wild poliovirus type 1 (WPV1) cases and districts where national nutrition survey (NNS) and serology were collected - Afghanistan, 2013.

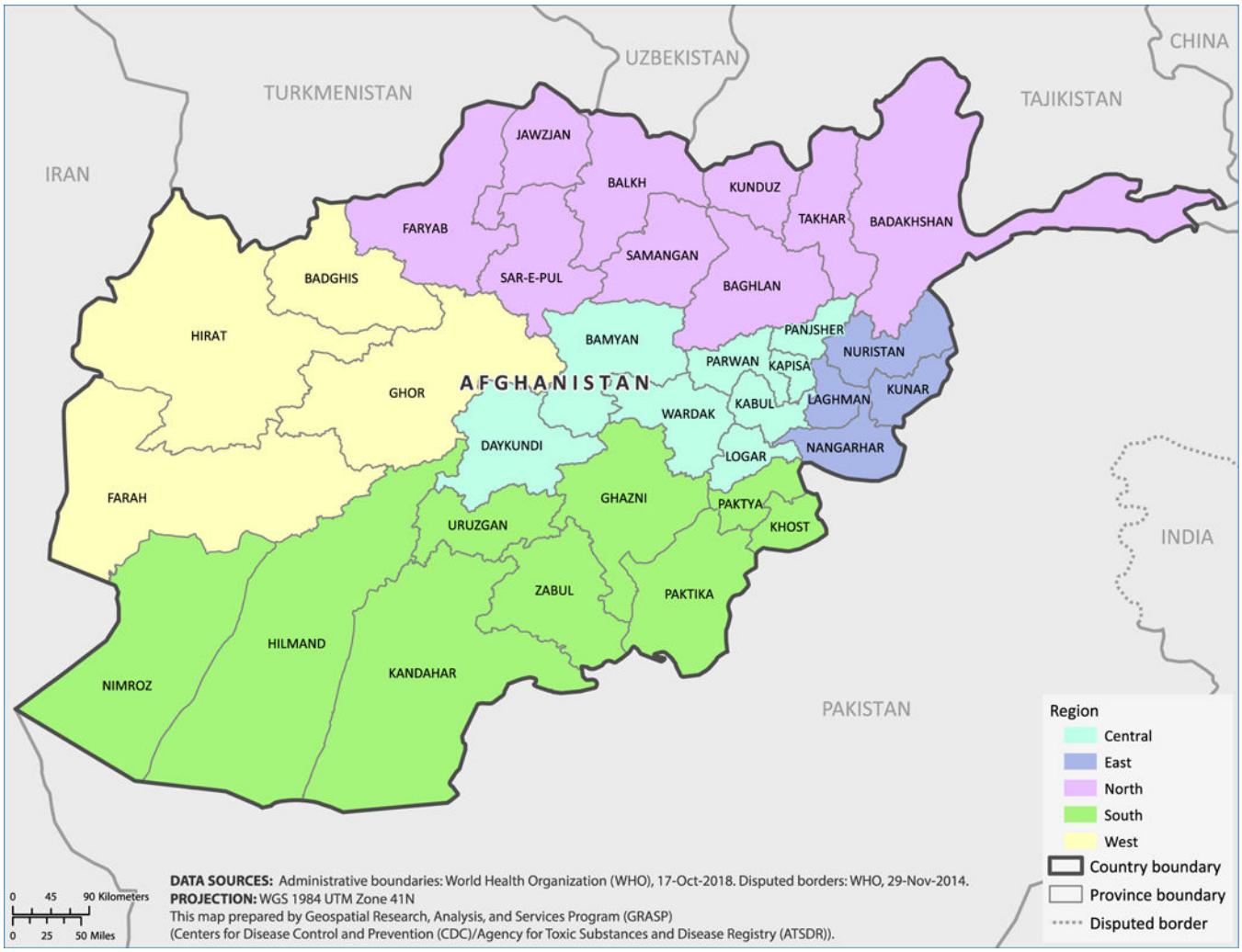

Fig. 2.
Regions and the respective provinces of Afghanistan.

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Table 1:

Demographic and nutritional characteristics of study population by available serum specimen (participants) and unavailable serum specimen (non-participants), unweighted results - Afghanistan, 2013.

	Overall N(%)	**Participants[a] N (%)**	**Non-participants[b] N (%)**	**p-value[c]**
Total	981 (100)	690 (70)	291 (30)	-
Gender				0.4
Male	508 (52)	351 (51)	157 (54)	
Female	473 (48)	339 (49)	134 (46)	
Age				0.2
6-11 months	152 (16)	112 (16)	40 (14)	
1-3 years	434 (44)	293 (42)	141 (48)	
4-5 years	395 (40)	285 (41)	110(38)	
Maternal education				0.7
llliterate	424 (43)	306 (44)	118 (41)	
Pre-/Religious/Some School	103 (10)	72 (10)	31 (11)	
High school or above	32 (3)	22 (3)	10(3)	
Missing	422 (43%)	290 (42)	132 (45)	
Diarrhea				0.009
Yes	211 (37)	136 (20)	75 (26)	
No	360 (63)	273 (40)	87 (30)	
Missing	410 (42)	281 (41)	129 (44)	
Weight-for-height				0.2
Adequately Nourished	783 (94)	565 (82)	235 (81)	
Acutely Malnourished[d]	52 (6)	44 (6)	13 (4)	
Missing	124 (13)	81 (12)	43 (15)	
Height-for-Age				0.4
Adequately Nourished	514 (62)	374 (54)	146 (50)	
Chronically Malnourished[e]	321 (38)	239 (35)	106(36)	
Missing	116 (12)	77 (11)	39 (13)	
Weight-for-Age				0.8

	Overall N(%)	Participants[a] N (%)	Non-participants[b] N (%)	p-value[c]
Adequately Nourished	666 (80)	485 (70)	199 (68)	
Underweight	169 (20)	129 (19)	56 (19)	
Missing	112 (11)	76(11)	36 (12)	
Hemoglobin				<0.0001
Adequate	502 (55)	376 (54)	126 (43)	
Anemic	407 (45)	247 (36)	160(55)	
Missing	72 (7)	67 (10)	5 (2)	
Region				
Central	204 (21)	145 (21)	59 (20)	<0.0001
East	98 (10)	86 (12)	12 (4)	
North	250 (25)	170(25)	80 (27)	
South	254 (26)	184 (27)	70 (24)	
West	175 (18)	105 (15)	70 (24)	

[a] Subjects for whom serum was available for microneutralization assay.

[b] Subjects for whom serum was not available for microneutralization assay.

[c] Chi-square test comparing participants and non-participants, with the missing values included as a category in the analysis.

[d] Stunting.

[e] Wasting.

Table 2:

Median antibody titer and seroprevalence for each poliovirus serotype - Afghanistan, 2013.

Serotype	Median titer [25th, 75th percentile]	% Seropositive (95% CI)[a]
Type 1	904 [369,1448]	99 (97,99)
Type 2	578 [180,1152]	98 (96,99)
Type 3	335 [86,861]	95 (93,96)
Seropositive for all 3		93 (91,95)
Seronegative for all 3		0.5 (0.2,1.7)

[a]CI:Confidence intervals.

Table 3:

Antibody seroprevalence to poliovirus serotypes 1, 2 and 3 by region - Afghanistan, 2013.

Region	No. PSUs[a]	Type 1 % Seropositive (95% CI)[b]	Type 2 % Seropositive (95% CI)	Type 3 % Seropositive (95% CI)
Central	20	99 (95,100)	99 (94,100)	96 (92,98)
East	6	98[c]	98	89
North	23	99 (95,100)	98 (95,99)	95 (88,98)
South	16	97 (92,99)	96 (88,99)	91 (83,96)
West	13	100 (98,100)	97 (89,99)	96 (90,98)

[a] PSU: Primary sampling unit.

[b] CI: Confidence interval.

[c] Too few primary sampling units to calculate a reliable confidence interval.

Table 4:

Poliovirus (PV) types 1,2 and 3 seroprevalence by demographic and nutritional status - Afghanistan, 2013.

	PV1 % (95% CI)[a]	PV2 % (95% CI)	PV3 % (95% CI)
Gender			
Male	99 (98,100)	99 (96,99)	96 (92,98)
Female	98 (95,99)	97 (94,99)	94 (89,96)
Age			
6-11 months	97 (89,99)	98 (95,99)	92 (85,96)
1-3 years	99 (98,100)	99 (98,100)	96 (93,98)
4-5 years	99 (95,100)	96 (91,98)	94 (89,96)
Hb[b]			
Adequate	98 (96,99)	97 (94,99)	94 (91,96)
Anemic	99 (98,100)	99 (95,100)	95 (92,97)
Diarrhea			
Yes	99 (95,100)	98 (92,99)	95 (89,98)
No	99 (96,99)	98 (95,99)	95 (91,97)
Weight-Height			
Adequately Nourished	98 (97,99)	98 (97,99)	95 (92,97)
Acutely Malnourished	100 (95,100)	96 (83,99)	94 (85,98)
Height-Age			
Adequately Nourished	99 (97,100)	98 (95,99)	95 (92,97)
Chronically Malnourished	98 (96,99)	98 (94,100)	95 (90,97)
Weight-Age			
Adequately Nourished	98 (97,99)	98 (96,99)	95 (92,97)
Underweight	100 (98,100)	98 (92,99)	95 (89,98)

[a] Cl: confidence interval.

[b] Hb: hemoglobin.