Supplementary Data

Consensus Middle East and North Africa Registry on Inborn Errors of Immunity

Figure S1- Compare Map of global all-cause disability-adjusted life years (DALYs) rate for 2019 and 1990 for both sexes below age 15 years [10].

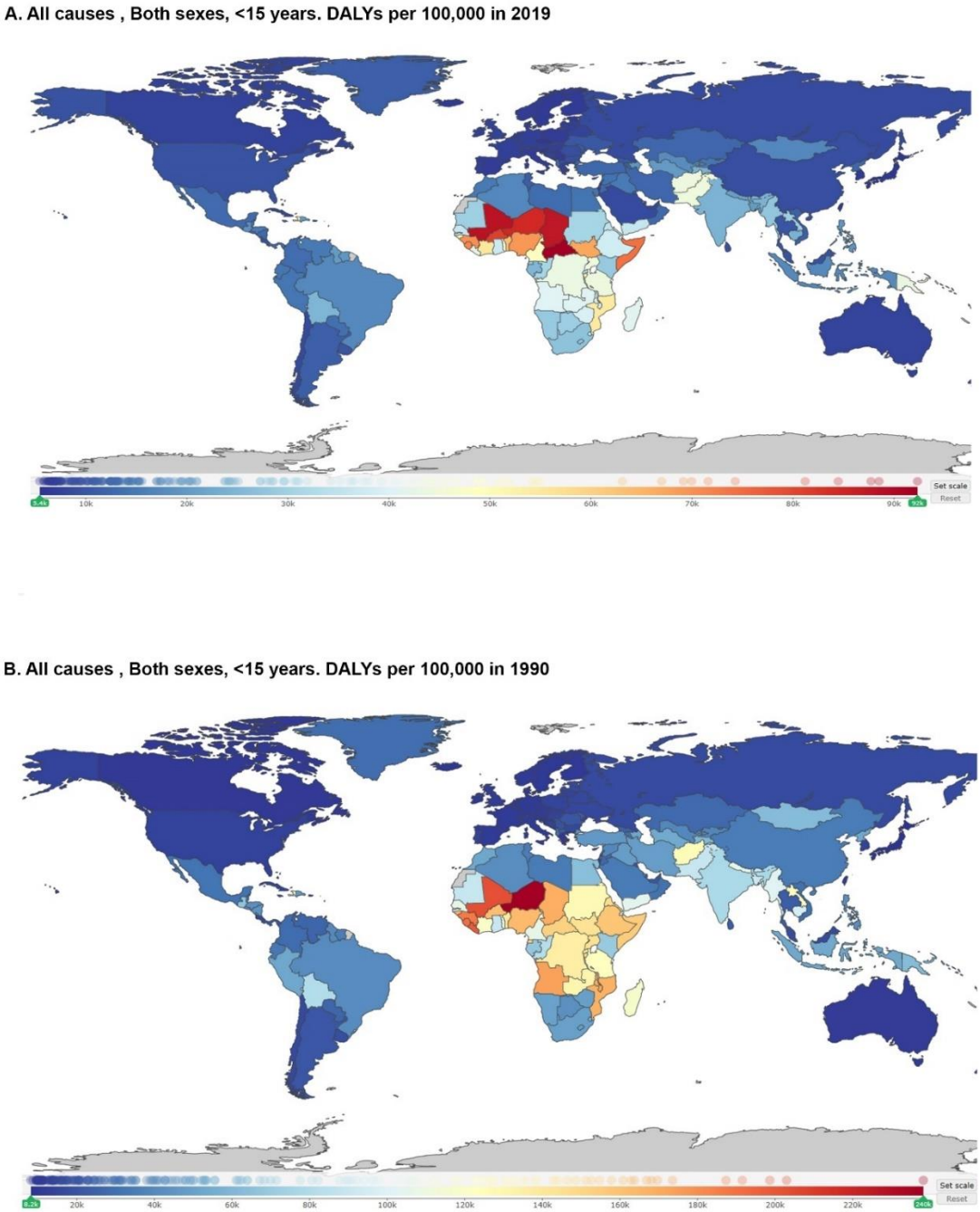


Figure S2- The trends of all-cause mortality rate and disability-adjusted life years (DALYs) rate from 2019 until 1990 for both sexes [10]. (A, B) Comparing Middle East and North Africa region with overall Global measures in three age categories of <1year, 1-4 years and 5-14 years. (C, D) Comparing different countries in the MENA regions.

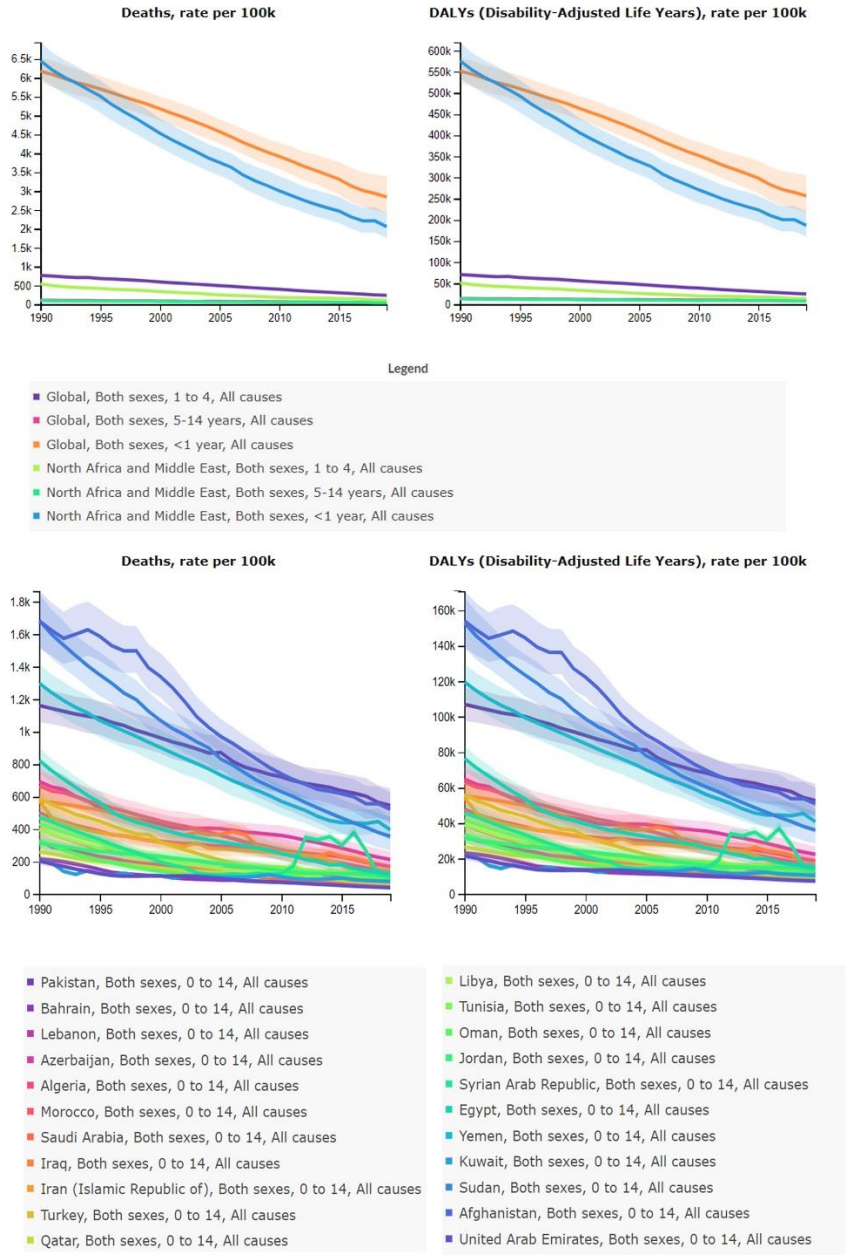


Figure S3- Trend of diagnosis of Inborn Errors of Immunity patients in the Middle East and North Africa region during 1984-2020. Delay in diagnosis was counted as lag between the onset of the first sign/symptom of the disease and the time of complete Inborn Errors of Immunity clinical diagnosis. Each dot represents one patient, blue line depicts the linear regression model and the gray zone accounted for 95% confidence interval.

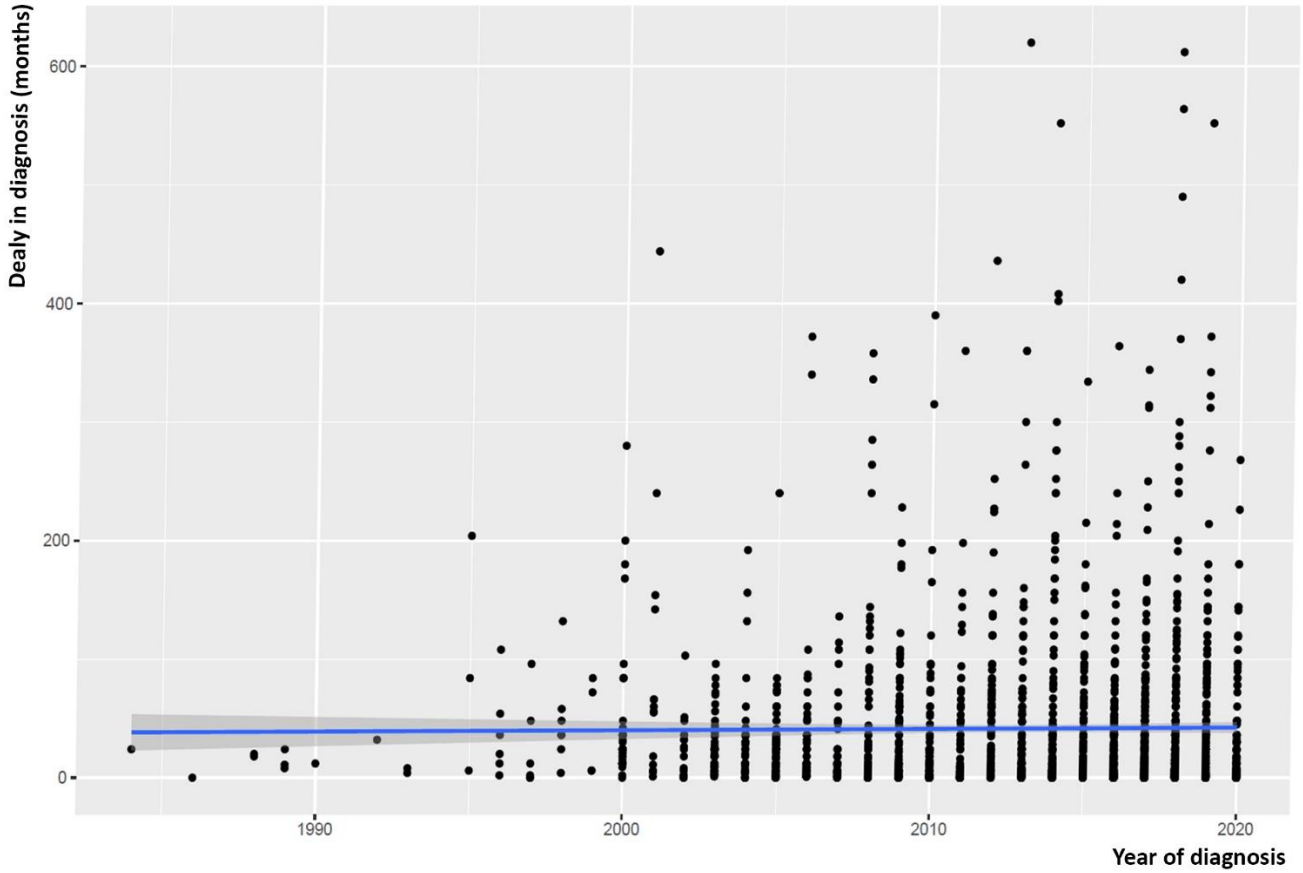


Figure S4- The association of rate of Inborn Errors of Immunity diagnosis and disease specific disability-adjusted life year (DALY)[10] of children including (A) upper respiratory infections, (B) lower respiratory infections, (C) enteropathies, (E) atopic disorders, (F) neoplasms and (D) other immune-related disorders in countries from Middle East and North Africa region.

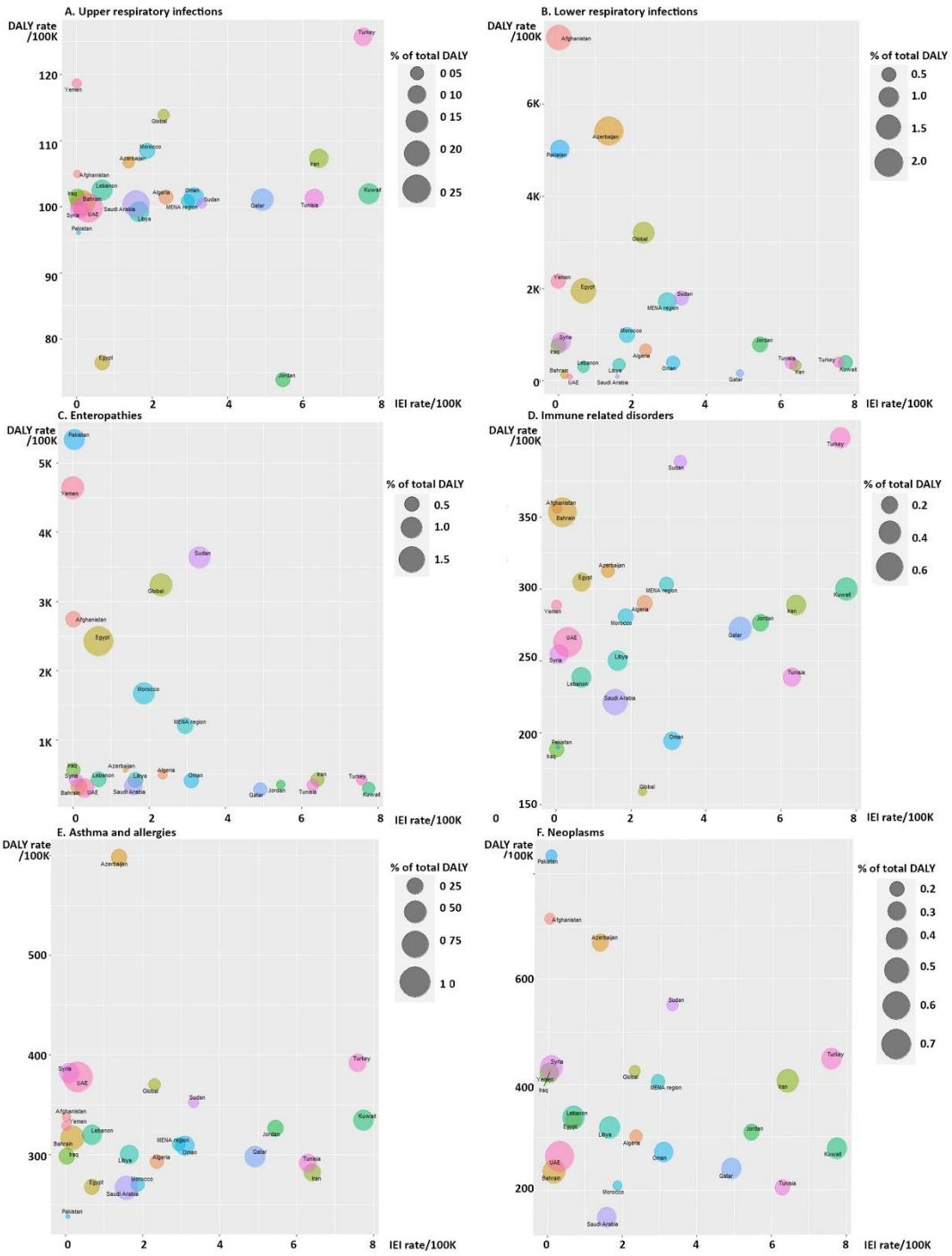


Figure S5- Trends of (A) clinical and (B) molecular diagnoses of Inborn Errors of Immunity in the Middle East and North Africa region during 2013-2020.

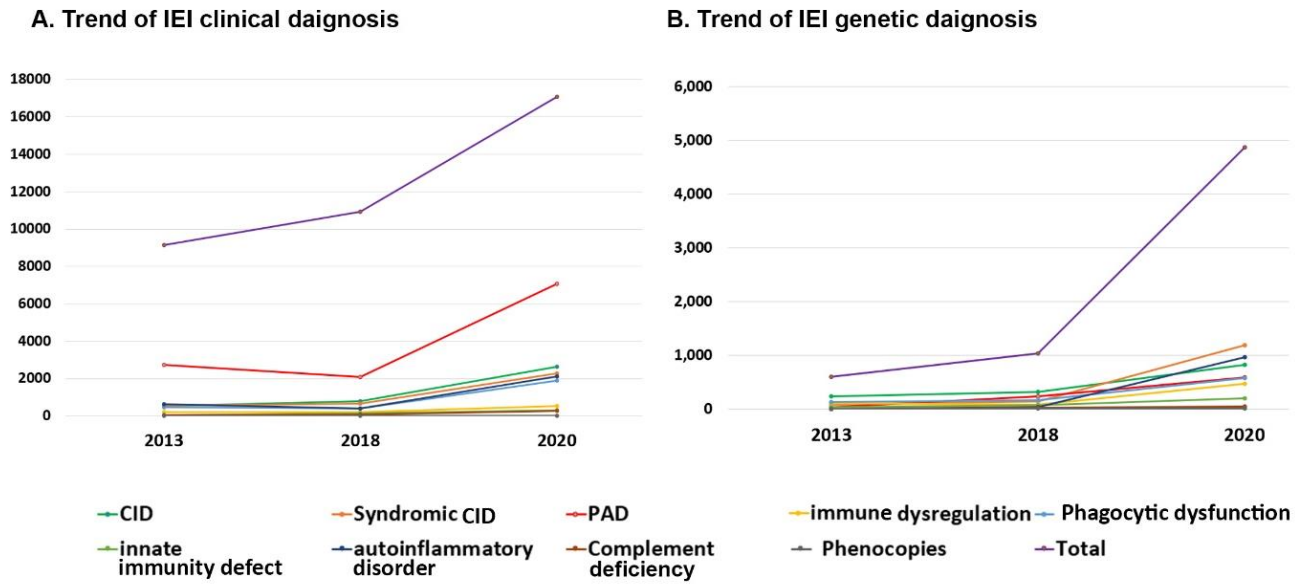
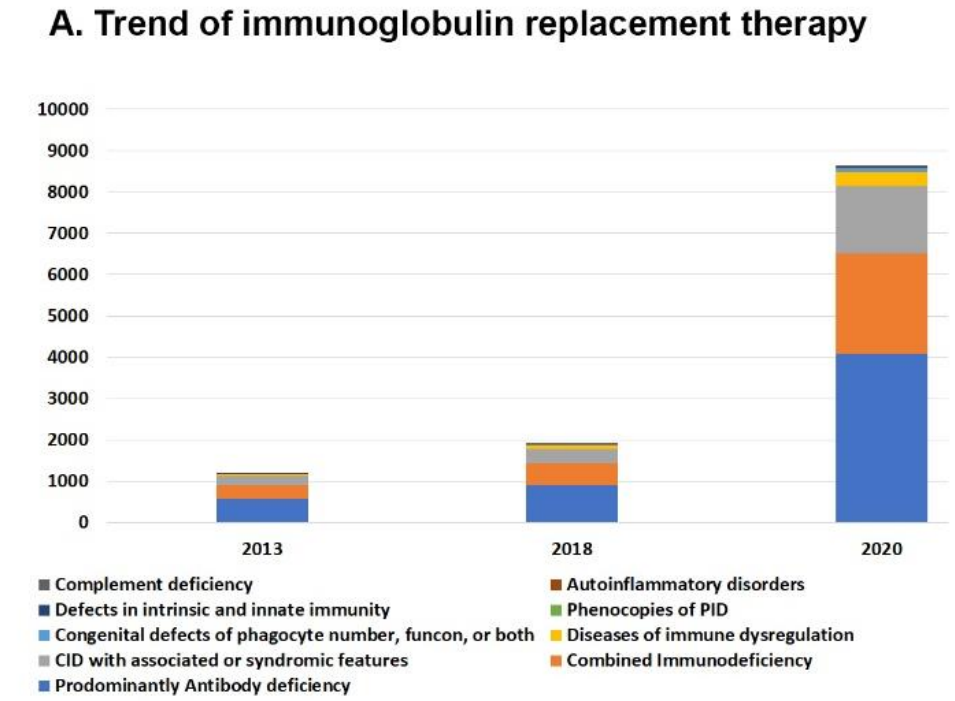


Figure S6- Trends of (A) immunoglobulin replacement and (B) hematopoietic stem cell transplantation therapies in the Middle East and North Africa region for Inborn Errors of Immunity patients during 2013 (11 countries registered) - 2020 (22 countries registered).



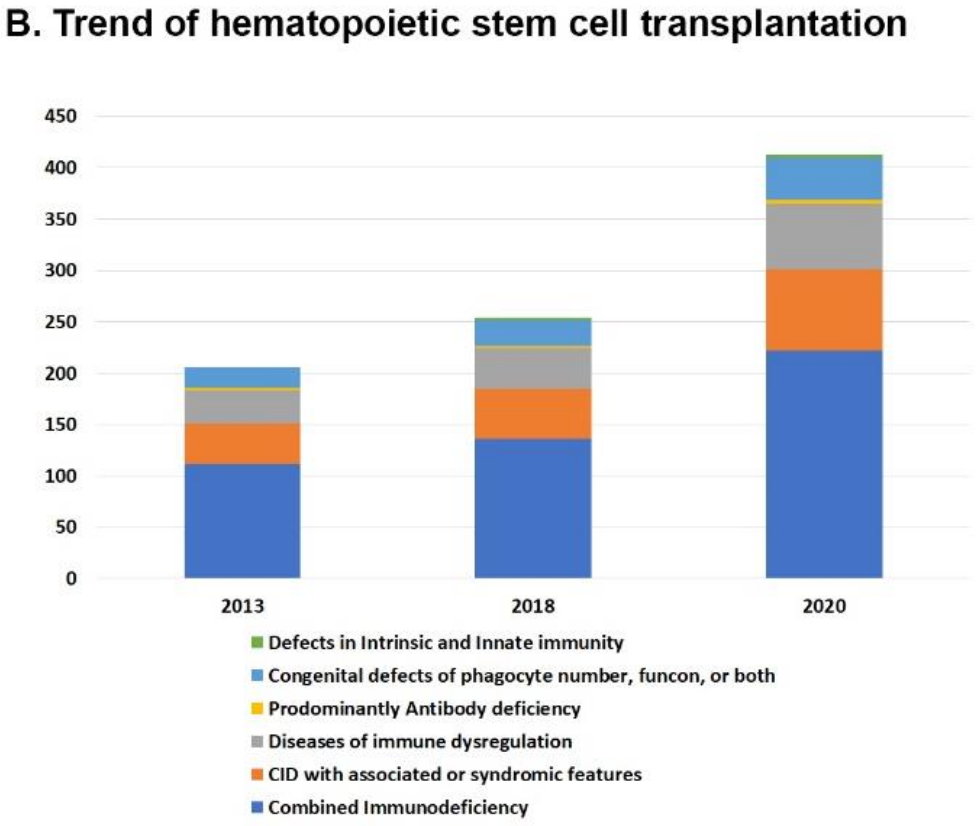


Table S1- International Statistical Classification of Diseases and Related Health Problems (ICD) code of immune-related disease included in the E chapter of Global Burden of Disease [10].

D codes group
D64.4, D64.8, D68- D68.6, D68.8- D68.9, D69- D69.4, D69.6, D69.8, D70- D70.4, D70.8- D70.9, D72- D72.1, D72.8- D72.9, D73- D73.5, D73.8- D73.9, D74.0, D74.8- D74.9, D75- D75.2,D75.8- D75.9, D76- D76.3, D80- D80.9, D81- D81.9, D82- D82.4, D82.8- D82.9, D83- D83.2, D83.8- D83.9,D84- D84.1, D84.8- D84.9, D86.8, D89- D89.2, D89.8- D89.9,
E codes group
E03- E03.1, E03.3- E03.5, E03.8- E03.9, E04- E04.2, E04.8- E04.9, E05- E05.5, E05.8- E05.9, E06- E06.3, E06.5, E06.9, E07- E07.1, E07.8- E07.9, E16.1- E16.4, E16.8- E16.9, E20- E20.1, E20.8- E20.9, E21- E21.5, E22- E22.2, E22.8- E22.9, E23.0, E23.2- E23.3,E23.6- E23.7, E24- E24.1, E24.3, E24.9, E25.0, E25.8- E25.9, E26- E26.1, E26.8- E26.9, E27- E27.2, E27.4- E27.5, E27.8- E27.9, E28- E28.1, E28.3, E28.8- E28.9, E29- E29.1, E29.8- E29.9, E30- E30.1, E30.8- E30.9, E31- E31.2, E31.8- E31.9, E32- E32.1, E32.8- E32.9, E34- E34.5, E34.8- E34.9, E67- E67.3, E67.8, E70- E70.5, E70.8- E70.9, E71- E71.5, E72- E72.5, E72.8- E72.9, E73- E73.1, E73.8- E73.9, E74- E74.4, E74.8- E74.9, E75- E75.6, E76- E76.3, E76.8- E76.9, E77- E77.1, E77.8- E77.9, E79- E79.2, E79.8- E79.9, E80- E80.7, E83- E83.9, E84- E84.9, E85- E85.9, E88- E88.9

Table S2. Novel Inborn Errors of Immunity identified by studying patients from the Middle East and North Africa region.

	Disease	Gene	Origin in MENA	Parental Consanguinity	Year of publication	Ref.
1.	**Immunodeficiencies affecting cellular and humoral immunity**					
1.	CD45 deficiency	*PTPRC*	Turkey	1	1997	PMID: 9068311
2.	LAT deficiency	*LAT*	Arab	1	2016	PMID: 27242165
3.	DNA PKcs deficiency	*PRKDC*	Turkey	1	2009	PMID: 19075392
4.	Cernunnos/XLF deficiency	*NHEJ1*	Turkey	1	2006	PMID:16439204
5.	CD40 deficiency	*CD40*	Turkey	1	2007	PMID:17502893
6.	MHC class I deficiency	*TAP2*	Morocco	1	1994	PMID:7517574
7.	MHC class II deficiency group A B C D	*CIITA*	North African	1	2001	PMID:11313409
8.	DOCK8 deficiency	*DOCK8*	Turkey	1	2014	PMID:14722525
9.	DOCK2 deficiency	*DOCK2*	Lebanon / Turkey/ Kuwait	1	2015	PMID:26083206
10.	STK4 deficiency	*STK4*	Turkey	1	2012	PMID:22174160
11.	TCRα deficiency	*TRAC*	Pakistan	1	2011	PMID: 21206088
12.	ITK deficiency	*ITK*	Arab	1	2011	PMID: 21109689
13.	MALT1 deficiency	*MALT1*	Lebanon	1	2013	PMID: 23727036
14.	IL-21 deficiency	*IL21*	Turkey	1	2014	PMID:24746753
15.	IL-21R deficiency	*IL21R*	Lebanon	1	2013	PMID:24746753
16.	OX40 deficiency	*TNFRSF4*	Turkey	1	2013	PMID: 23897980
17.	TFRC deficiency	*TFRC*	Kuwait	1	2016	PMID: 26642240
18.	c-Rel deficiency	*REL*	Kuwait	1	2019	PMID: 31103457
19.	FCHO1 deficiency	*FCHO1*	Turkey /Algeria	*unknown*	2019	PMID: 30822429
20.	PAX1 deficiency	*PAX1*	Morocco/ Saudi Arabia	1	2020	PMID: 32111619
2.	**Combined immunodeficiencies with associated or syndromic features**					
21.	WIP deficiency	*WIPF1*	Morocco	1	2012	PMID: 22231303
22.	Ataxia-telangiectasia	*ATM*	Arab	*unknown*	1992	PMID: 1551665
23.	Immunodeficiency with centromeric instability and facial anomalies (ICF 3)	*CDCA7*	Turkey	*1*	2015	PMID:26216346
24.	Immunodeficiency with centromeric instability and facial anomalies (ICF types4)	*HELLS*	Turkey	1	2015	PMID:26216346
25.	POLE2 (Polymerase ε subunit 2) deficiency	*POLE2*	Saudi Arabia	1	2017	PMID: 26365386
26.	ERCC6L2 (Hebo deficiency)	*ERCC6L2*	Pakistan	1	2014	PMID:24507776
27.	MYSM1 deficiency	*MYSM1*	Saudi Arabia	1	2013	PMID: 24288411
28.	MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	Lebanon	0	2011	PMID: 21977988
29.	ZNF341 deficiency AR-HIES	*ZNF341*	Arab	1	2018	PMID: 29907690
30.	Comel-Netherton syndrome	*SPINK5*	Pakistan/ Turkey	1	2002	PMID: 11841556
31.	PGM3 deficiency	*PGM3*	Egypt	1	2014	PMID: 24589341
32.	Transcobalamin 2 deficiency	*TCN2*	Lebanon/ Turkey	1	2009	PMID: 19373259
33.	SLC46A1/PCFT deficiency causing hereditary folate malabsorption	*SLC46A1*	Tunisia	*unknown*	2001	PMID: 11804211
34.	Tricho-Hepato-Enteric Syndrome (THES)	*TTC37*	Pakistan /Kurdish	1	2010	PMID: 20176027
35.	Tricho-Hepato-Enteric Syndrome (THES)	*SKIV2L*	North Africa / Turkey	1	2012	PMID: 22444670
36.	Hepatic veno-occlusive disease with immunodeficiency (VODI)	*SP110*	Lebanon	1	2006	PMID: 16648851
37.	EPG5 deficiency (Vici syndrome)	*EPG5*	Arab / Turkey	1	2013	PMID: 23222957
38.	HOIP deficiency	*RNF31*	Kuwait	1	2015	PMID: 26008899
39.	Hennekam-lymphangiectasia-lymphedema syndrome	*CCBE1*	Oman/ Iraq	1	2009	PMID:19935664
40.	Activating de novo mutations in nuclear factor erythroid 2- like (NFE2L2)	*NFE2L2*	Qatar	0	2017	PMID: 29018201
41.	IL6ST deficiency	*IL6ST-AR*	Saudi Arabia	1	2019	PMID: 31130284
3.	**Predominantly antibody deficiencies**					
42.	μ heavy chain deficiency	*IGHM*	Turkey	1	1996	PMID: 8890099
43.	Igα deficiency	*CD79A*	Turkey	0	1999	PMID: 10525050
44.	CD19 deficiency	*CD19*	Turkey	1	2006	PMID: 16672701
45.	CD81 deficiency	*CD81*	Morocco	1	2010	PMID: 20237408
46.	CD20 deficiency	*CD20*	Turkey	1	2010	PMID: 20038800
47.	TRNT1 deficiency	*TRNT1*	Pakistan	1	2014	PMID: 25193871
48.	ATP6AP1 deficiency	*ATP6AP1*	Tunisia	1	2016	PMID: 27231034
49.	AID deficiency	*AICDA*	Morocco / Turkey	1	2000	PMID: 11007475
50.	FNIP1 deficiency	*FNIP1*	Turkey/ Kurdish	1	2020	PMID: 32181500
4.	**Diseases of immune dysregulation**					
51.	UNC13D/Munc13–4 deficiency (FHL3)	*UNC13D*	Morocco	1	2003	PMID: 14622600

52.	Syntaxin 11 deficiency (FHL4)	*STX11*	Kurdish	1	2005	PMID: 15703195
53.	STXBP2/Munc18–2 deficiency (FHL5)	*STXBP2*	Saudi Ara/ Turkey	1	2009	PMID: 19804848
54.	Chediak-Higashi syndrome	*LYST*	Kuwait/ Turkey	1	1997	PMID: 9215679
55.	Griscelli syndrome type 2	*RAB27A*	Turkey	1	2000	PMID: 10835631
56.	Hermansky-Pudlak syndrome type 10	*AP3D1*	Turkey	1	2016	PMID: 26744459
57.	LRBA deficiency	*LRBA*	Arab / Iran	1	2012	PMID: 22608502
58.	DEF6 deficiency	*DEF6*	Pakistan/ Iraq	1	2019	PMID: 31308374
59.	FERMT1 deficiency	*FERMT1*	North African	1	2003	PMID: 12668616
60.	Prolidase deficiency	*PEPD*	Middle east	0	1990	PMID: 2365824
61.	IL-10R deficiency	*IL10RA*	Lebanon	1	2009	PMID: 19890111
62.	TGFB1 deficiency	*TGFB1*	Pakistan	1	2018	PMID: 29483653
63.	RIPK1	*RIPK1*	Pakistan	1	2018	PMID: 30026316
64.	FADD deficiency	*FADD*	Pakistan	1	2010	PMID: 21109225
65.	CD27 deficiency	*CD27*	Morocco	1	2012	PMID: 22197273
66.	CD70 deficiency	*CD70*	Egypt/ Turkey/ Iran	1	2017	PMID:28011863
67.	RASGRP1 deficiency	*RASGRP1*	Turkey	1	2016	PMID: 27776107
68.	RLTPR deficiency	*CARMIL2*	Morocco/ Tunisia/ Turkey	1	2016	PMID: 27647349
69.	PRKCD deficiency	*PRKCD*	Turkey	1	2013	PubMed: 23319571
5.	**Congenital defects of phagocyte number or function**					
70.	HAX1 deficiency (Kostmann Disease) (SCN3)	*HAX1*	Kurdish / Turkey/ Iran/ Lebanon	1	2007	PMID: 17187068
71.	G6PC3 deficiency (SCN4)	*G6PC3*	Turkey	1	2009	PMID: 19118303
72.	VPS45 deficiency (SCN5)	*VPS45*	Arab	1	2013	PMID: 23738510
73.	JAGN1 deficiency	*JAGN1*	Algeria/ Iran/ Turkey Morocco/ Pakistan	1	2014	PMID: 25129144
74.	3-Methylglutaconic aciduria	*CLPB*	Turkey	0	2015	PMID: 25597510 PMID: 25597511 PMID: 25650066
75.	SMARCD2 deficiency	*SMARCD2*	Pakistan/ Lebanon	1	2017	PMID: 28369036
76.	Shwachman-Diamond Syndrome	*DNAJC21*	Algeria /Pakistan	1	2016	PMID: 12496757
77.	Shwachman-Diamond Syndrome	*EFL1*	Arab	1	2017	PMID: 28331068
78.	Leukocyte adhesion deficiency type 2 (LAD2)	*SLC35C1*	Turkey /Arab	*unknown*	2001	PMID: 11326279
79.	Leukocyte adhesion deficiency type 3 (LAD3)	*FERMT3*	Turkey	1	2007	PMID: 17185466
80.	Papillon-Lefèvre syndrome	*CTSC*	Egypt / Pakistan/ Lebanon	1	1999	PMID: 10581027
81.	WDR1 deficiency	*WDR1*	Qatar	1	2016	PMID: 27557945
82.	Autosomal recessive CGD	*CYBC1*	Saudi Arabia	1	2017	PMID: 28600779
6.	**Defects in intrinsic and innate immunity**					
83.	IL-12 and IL-23 receptor β1 chain deficiency	*IL12RB1*	Turkey	1	1998	PMID: 9603733
84.	IL-12p40 (IL-12 and IL-23) deficiency	*IL12B*	Pakistan	1	1998	PMID: 9854038
85.	ISG15 deficiency	*ISG15*	Turkey /Iran	1	2012	PMID: 22859821
86.	RORγt deficiency	*RORC*	Saudi Arabia	1	2015	PMID: 26160376
87.	EVER1 deficiency	*TMC6*	Algeria	1	2002	PMID: 12426567
88.	EVER2 deficiency	*TMC8*	Algeria	1	2002	PMID: 12426567
89.	CIB1 deficiency	*CIB1*	Iran	1	2018	PMID: 30068544
90.	IRF9 deficiency	*IRF9*	Algeria	1	2018	PMID: 30143481
91.	IFNAR1 deficiency	*IFNAR1*	Iran	1	2019	PMID: 31270247
92.	TRIF deficiency	*TICAM1*	Saudi Arabia	1	2011	PMID: 22105173
93.	DBR1 deficiency	*DBR1*	Arab	1	2018	PMID: 29474921
94.	CARD9 deficiency	*CARD9*	Iran	1	2009	PMID: 19864672
95.	IL-17RC deficiency	*IL17RC*	Turkey	1	2015	PMID: 25918342
96.	IRAK4 deficiency	*IRAK4*	Saudi Arabia	1	2003	PMID: 12637671
97.	MyD88 deficiency	*MYD88*	Turkey	1	2008	PMID: 18669862
98.	Osteopetrosis	*TNFSF11*	Tunisia/ Kurdish	1	2007	PMID: 17632511
99.	Osteopetrosis	*SNX10*	Arab	1	2012	PMID: 22499339
100.	Osteopetrosis	*TCIRG1*	Turkey	1	2000	PMID: 10942435
101.	IL-18BP deficiency	*IL18BP*	Algeria	1	2019	PMID: 31213488
102.	IFNγ deficiency	*IFNG*	Kuwait	1	2020	PMID: 32163377
103.	TBX21 deficiency	*TBX21*	Morocco/ Qatar	1	2020	PMID: 33296702
104.	NOS2 deficiency	*NOS2*	Iran	1	2020	PMID: 31995689
105.	SNORA31 deficiency	*SNORA31*	Morocco/ Saudi Arabia	1	2019	PMID: 31806906

7.	**Autoinflammatory disorders**					
106.	STING-associated vasculopathy infantile-onset (SAVI)	*TMEM173*	Turkey	*unknown*	2014	PMID: 25029335
107.	TREX1 deficiency Aicardi-Goutieres syndrome 1(AGS1)	*TREX1*	Pakistan/ Turkey	1	2006	PMID: 16845398
108.	RNASEH2B deficiency AGS2	*RNASEH2B*	Morocco/ Algeria/ Tunisia	1	2006	PMID: 16845400
109.	RNASEH2C deficiency AGS3	*RNASEH2C*	Pakistan	1	2006	PMID: 16845400
110.	SAMHD1 deficiency AGS5	*SAMHD1*	Pakistan /Morocco/ Arab	1	2009	PMID: 19525956
111.	Pediatric systemic lupus erythematosus due to DNASE1L3 deficiency	*DNASE1L3*	Arab	1	2011	PMID: 22019780
112.	Spondyloenchondro-dysplasia with immune dysregulation(SPENCD)	*ACP5*	Turkey/ Pakistan / Egypt	1	2011	PMID: 21217755
113.	USP18 deficiency	*USP18*	Turkey	1	2016	PMID: 27325888
114.	Familial Mediterranean fever	*MEFV*	Iraq /North African	*unknown*	1997	PMID: 9288758
115.	NLRP1 deficiency	*NLRP1*	Algeria	1	2016	PMID: 27965258
116.	ADAM17 deficiency	*ADAM17*	Lebanon	1	2011	PMID: 22010916
117.	Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	*LPIN2*	Jordan	1	2005	PMID: 15994876
118.	DIRA (Deficiency of the Interleukin 1 Receptor Antagonist)	*IL1RN*	Lebanon	1	2009	PMID: 19494218
119.	DITRA (Deficiency of IL-36 receptor antagonist)	*IL36RN*	Tunisia	1	2011	PMID: 21848462
120.	SLC29A3 mutation	*SLC29A3*	Arab	1	2008	PMID: 18940313
121.	Otulipenia/ORAS	*OTULIN*	Pakistan	1	2016	PMID: 27523608
122.	A20 deficiency	*TNFAIP3*	Turkey	*unknown*	2016	PMID: 26642243
123.	T cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency)	*HAVCR2*	North African	*unknown*	2018	PMID: 30374066
124.	STAT2 gain of function	*STAT2*	Morocco	1	2020	PMID: 32092142
125.	HEM1 deficiency	*NCKAP1L*	Iran /UAE/ Saudi Arabia	1	2020	PMID: 32647003/ PMID: 32646852/ PMID: 32766723
8.	**Complement deficiencies**					
126.	C1q deficiency due to defects	*C1QA*	Iraq / Turkey / Sudan	1	2011	PMID: 21654842
127.	C1q deficiency due to defects	*C1QB*	Morocco	1	2011	PMID: 21654842
128.	C1q deficiency due to defects	*C1QC*	Saudi Arabia/ Pakistan/ Turkey	1	2011	PMID: 21654842
129.	Membrane Cofactor Protein (CD46) deficiency	*CD46*	Turkey	1	2003	PMID: 14566051
130.	CD55 deficiency (CHAPEL disease)	*CD55*	Turkey /Morocco /Syria / Arab	1	2017	PMID: 28657829 PMID: 28657861
9.	**Bone marrow failure**					
131.	Fanconi anemia type E	*FANCE*	Turkey	*unknown*	2000	PMID: 11001585
132.	Fanconi anemia type G	*XRCC9*	Arab	1	1998	PMID: 9806548
133.	Fanconi anemia type I	*FANCI*	Turkey	1	2007	PMID: 17452773
134.	Fanconi anemia type N	*PALB2*	Morocco	*unknown*	2007	PMID: 17200671
135.	Fanconi anemia type O	*RAD51C*	Pakistan	1	2010	PMID: 20400963
136.	Fanconi anemia type U	*XRCC2*	Saudi Arabia	1	2012	PMID: 22232082
137.	Dyskeratosis congenita, DKCB1	*NOLA3*	Saudi Arabia	1	2007	PMID: 17507419
138.	Dyskeratosis congenita, DKCB2	*NOLA2*	Turkey	1	2008	PMID: 18523010
139.	Dyskeratosis congenita, DKCB4	*TERT*	Iran/ Libya	1	2007	PMID: 17785587
140.	Dyskeratosis congenita, DKCB6	*PARN*	Pakistan	1	2015	PMID: 25893599
141.	Coats plus syndrome	*STN1*	Arab	1	2016	PMID: 27432940
142.	Coats plus syndrome	*CTC1*	Egypt	1	2012	PMID: 22267198

0: non-consanguineous marriage, 1: consanguineous marriage

Table S3- Comparison of Inborn Errors of Immunity epidemiological indexes among different regional and continental registers.

Reigon/ Country	Population at year of report	Registered Patients	Year of report	PAD (%)	CID (%)	Phagocytic defects (%)	Complement deficiency (%)	Other PIDs (%)	Confirmed genetic diagnosis (%)	Gender ratio M/F	Consanguinity (%)
Total MENA (Current study)	578,000,000	17120	2020	41.2	15.4	11.0	1.6	30.8	4873 (28.4)	1.5	60.5
Total Asia [2]	464,452067	15939	2020	41.9	20.4	13.8	3.5	20.3	3161 (25.9)	2.2	20.8
Total Oceania [2]	42669777	1876	2020	77.4	8.9	3.2	5.9	4.6	223 (11.8)	1.1	NR
Total Africa [2]	1339849038	4509	2020	22.0	27.4	17.7	1.6	30.9	250 (5.5)	1.3	54.9
Total Europe [2]	747632000	40223	2020	53.9	11.3	9.0	13.0	12.6	6239 (15.5)	0.7	3.4
Total America [2]	1001000000	42067	2020	56.0	5.2	5.0	2.3	31.3	3979 (9.4)	2.5	0.5
Total World [2]	7800000000	104614	2020	51.9	10.8	8.3	6.6	22.1	13852 (13.2)	1.5	6.2