



Import of Global MRSA Clones into Europe

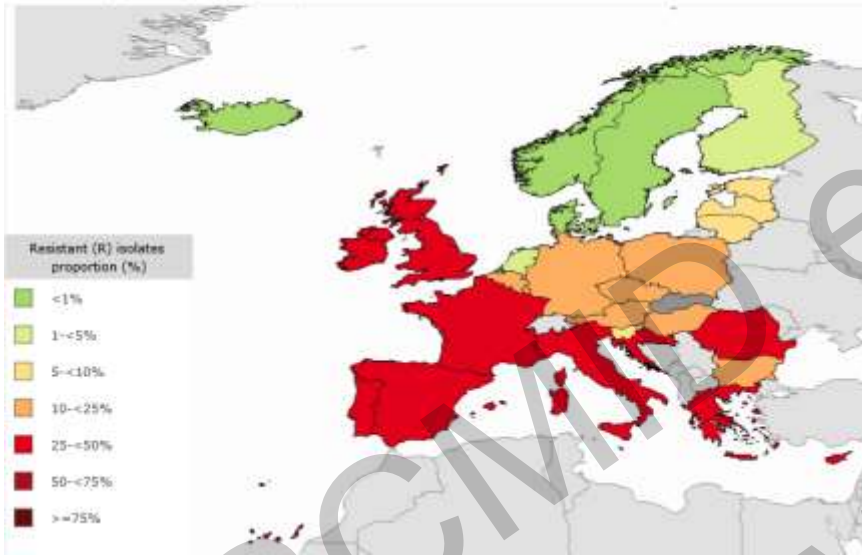
Anders Rhod Larsen

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Staphylococci

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 **Surveillance Atlas of Infectious Diseases**

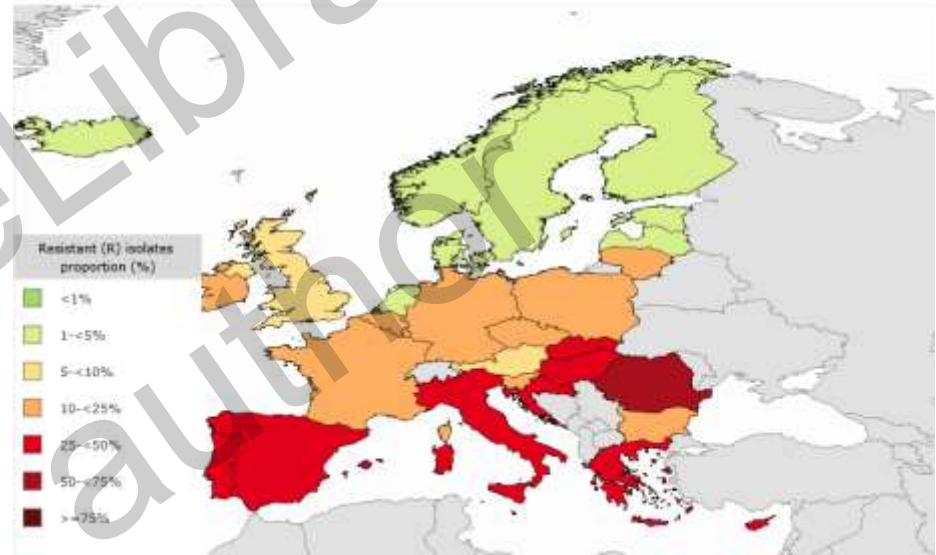
Antimicrobial resistance | Staphylococcus aureus | **Meticillin (MRSA)**
Resistant (R) isolates proportion | 2007



2007

 **Surveillance Atlas of Infectious Diseases**

Antimicrobial resistance | Staphylococcus aureus | **Meticillin (MRSA)**
Resistant (R) isolates proportion | 2016

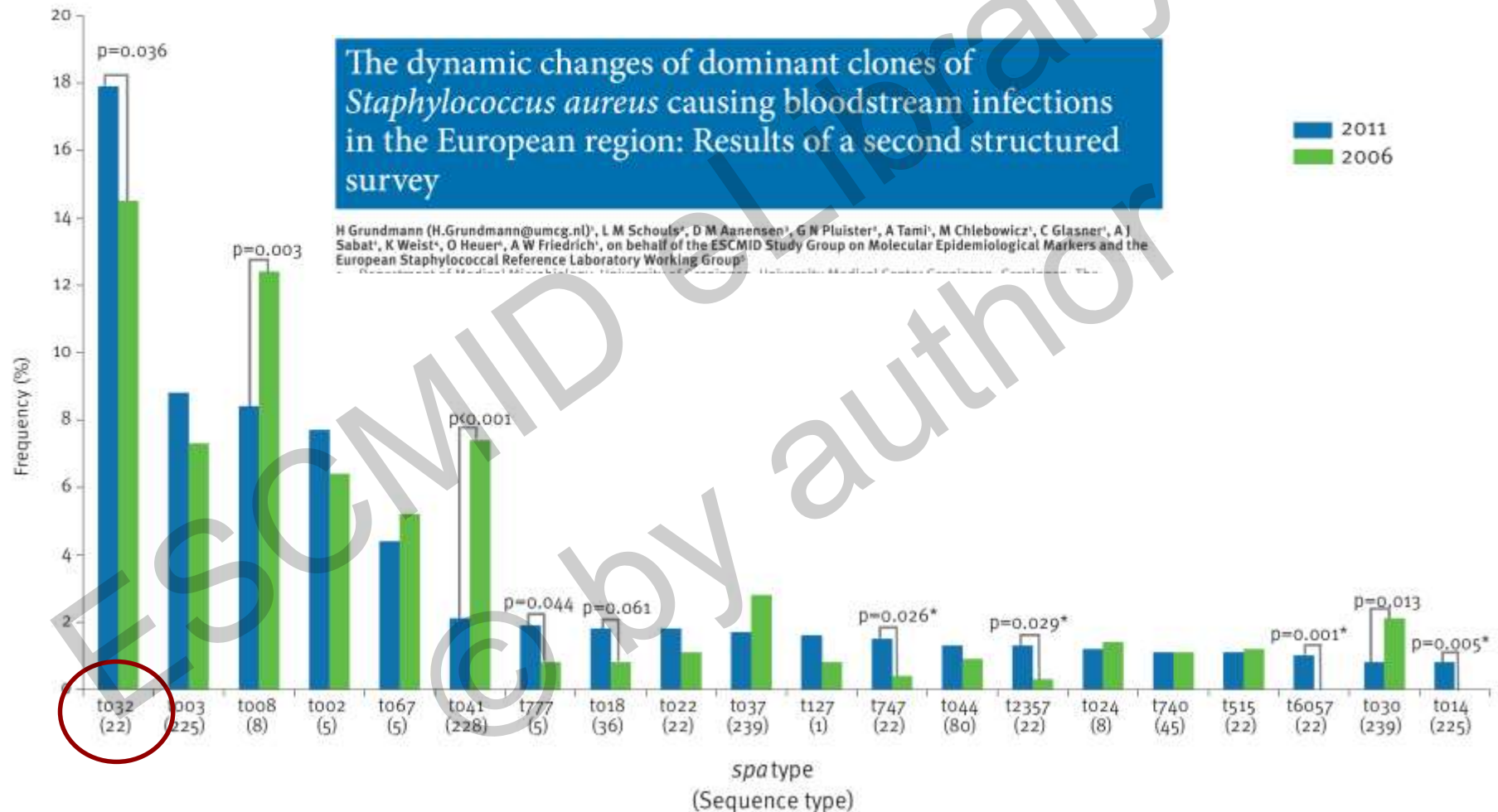


2016

- Decrease in HA-MRSA, improved infection control
 - UK from 35.6 to 6.7%; France 25.8 to 13.8% among others ..
- Nordic countries has increased MRSA prevalence

FIGURE 2

Comparison of meticillin-resistant *Staphylococcus aureus* *spa*-type frequencies, 2011 and 2006



Hospital aquired (HA)



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Hospital acquired (HA)



Community acquired (CA)



Livestock associated (LA)

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Hospital acquired (HA)



Community acquired (CA)



Livestock associated (LA)



Imported (Imp)

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❖ Immigration

- Immigrants and refugees

❖ Travel

- With hospital contact
- Without hospital contact = community acquisition

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❖ Immigration

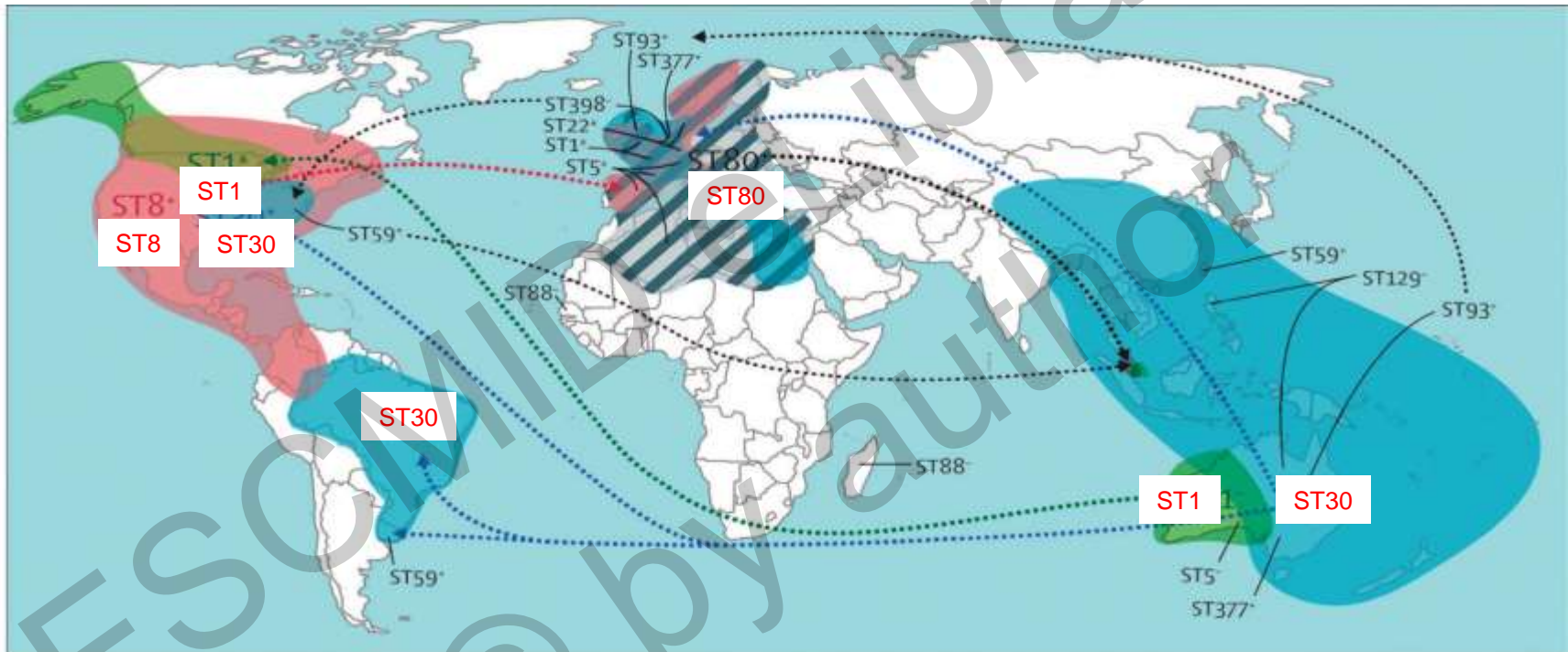
- 10.3% of refugees were tested positive at hospital admission (*Reinheimer et al. BMC Infectious Diseases,2017*)

❖ Travel

- With hospital contact
 - Medical tourists 5.9% (*Reinheimer et al. BMC Infectious Diseases,2017*)
- Without hospital contact = community acquisition
 - ?

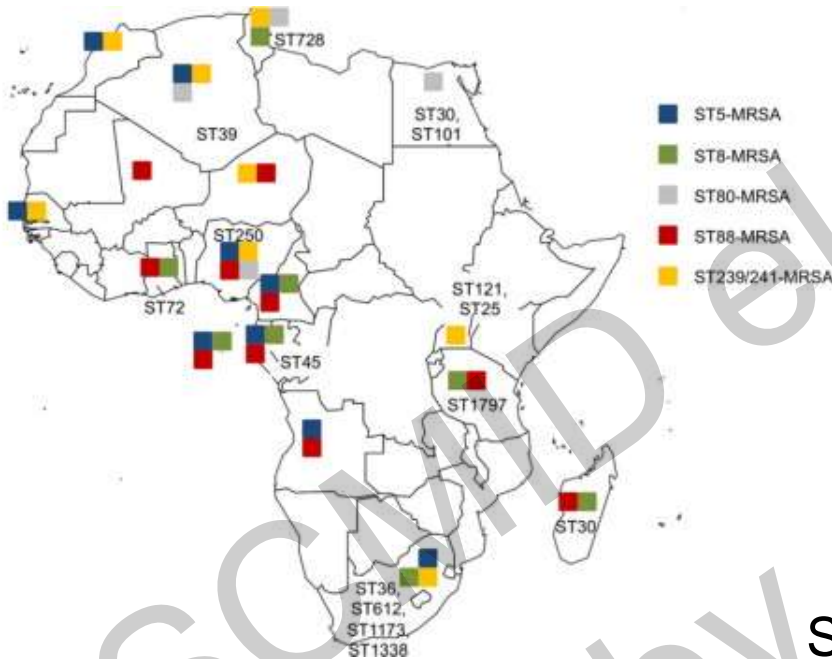
- **CA-MRSA** emerged globally in the mid- 1990s, characterized by
 - smaller SCCmec elements (type IV and V)
 - **PVL genes *lukS/F-pv***, associated with severe skin infections and necrotizing pneumonia (*Tristan A. et al. Emerg Infect Dis. 2007, Lina G, et al. Clin Infect Dis 1999*)
- CA- MRSA are more diverse than HA-MRSA and with **regional clustering**
 - **European CA- MRSA, ST80-IV** linked to **Greece, North Africa and Middle East** (*Drougka E et al. J Clin Microbiol. 2014; Troikian, Clin Microbiol Infect 2014*).
 - **USA300, ST8-IV, t008** linked to import from the **USA** (*Larsen AR. et al., Eurosurv.2007*)
 - **South West Pacific CA-MRSA, ST30-IV** associated with travel in **Phillipines** (*Bochet, MJ et. Al., Travel Med. 2008*).

Community-acquired MRSA



Deleo, Lancet, 2010;375:1577

MRSA in Africa and the Indian subcontinent



Bangladesh,
Bhutan,
India,
Maldives,
Nepal,
Pakistan
Sri Lanka

ST772-V, PVL+ Bengal Bay CA-MRSA
ST22-IV, PVL+

Tong S, Kearns S. Lancet Infectious Diseases 2013

ST80-IV in Northern Africa
ST88-IV in Central Africa

F. Schaumburg et al. , Clin Microbiol Infect 2014

- ❖ Different waves of immigration from different areas of the world
- ❖ Recent years, Europe has received immigrants from the civil- war in Syria
 - In 2015, Germany reported the largest total number of immigrants (1 543 800), followed by
 - The United Kingdom (631 500),
 - France (363 900),
 - Spain (342 100) and
 - Italy (280 100)

Eurostat:

<http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00176&plugin=1>

Foreign-born Population, 1 January 2016

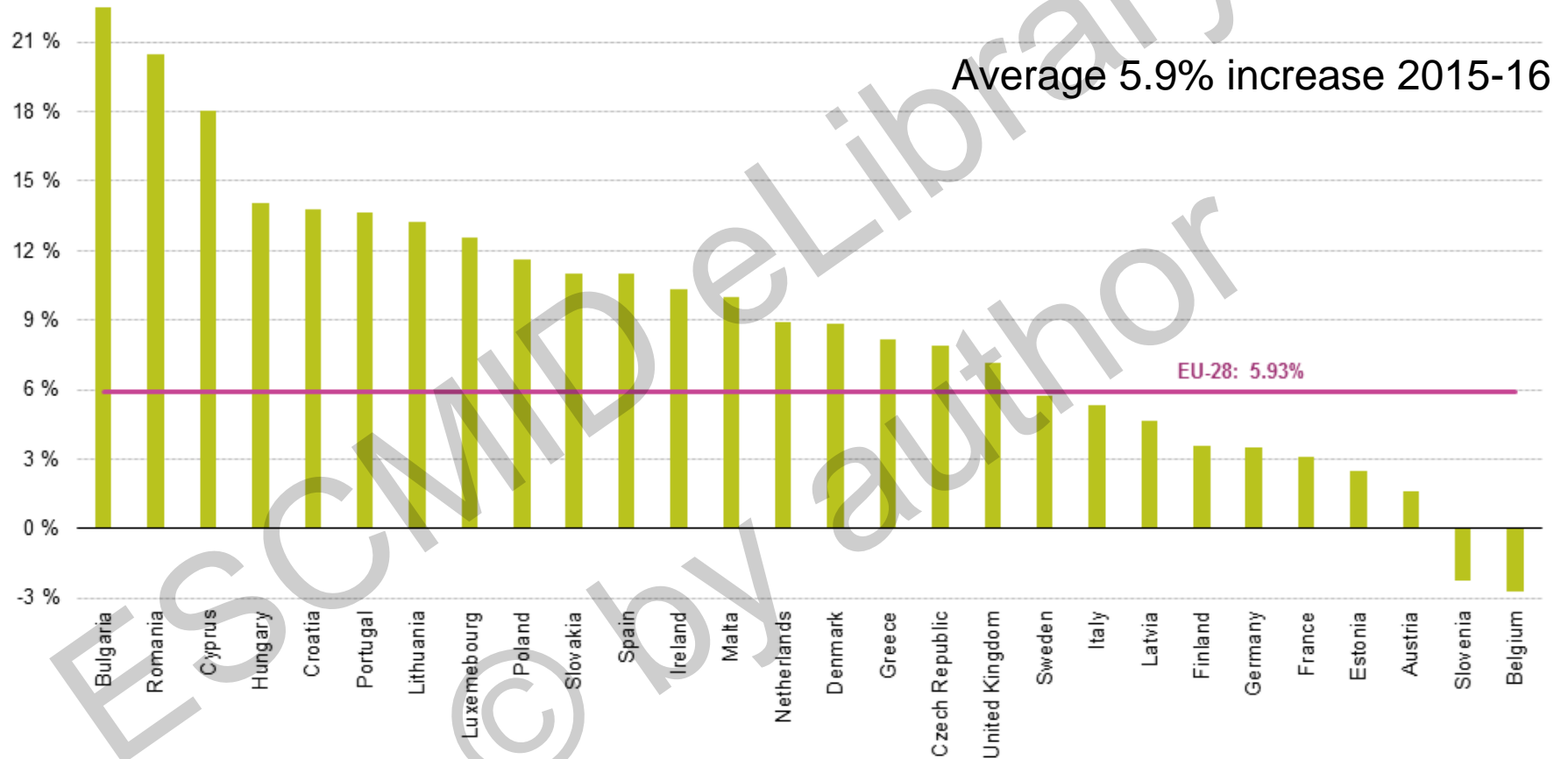
	Total		Born in another EU Member State		Born in a non-member country	
	(thousands)	(% of the population)	(thousands)	(% of the population)	(thousands)	(% of the population)
Belgium	1 845.6	16.3	866.8	7.7	978.8	8.7
Bulgaria	136.4	1.9	48.5	0.7	87.9	1.2
Czech Republic	433.3	4.1	171.8	1.6	261.5	2.5
Denmark	636.7	11.2	216.9	3.8	419.8	7.4
Germany	10 908.3	13.3	4 351.8	5.3	6 556.4	8.0
Estonia	193.8	14.7	19.2	1.5	174.6	13.3
Ireland	798.6	16.9	547.6	11.6	251.0	5.3
Greece	1 220.4	11.3	350.1	3.2	870.3	8.1
Spain	5 919.2	12.7	1 957.0	4.2	3 962.2	8.5
France	7 902.8	11.8	2 203.8	3.3	5 699.0	8.5
Croatia	547.9	13.1	88.6	1.6	479.4	11.4
Italy	5 907.5	9.7	1 823.8	3.0	4 083.6	6.7
Cyprus	172.8	20.4	110.4	13.0	62.4	7.4
Latvia	258.9	13.1	27.6	1.4		
Lithuania	129.7	4.5	20.8	0.7		
Luxembourg	260.6	45.2	194.8	33.8		
Hungary	503.8	5.1	320.5	3.3	183.3	1.9
Malta	45.9	10.6	20.7	4.8	25.1	5.8
Netherlands	2 056.5	12.1	554.9	3.3	1 501.6	8.8
Austria	1 578.2	18.2	713.6	8.2	864.6	9.9
Poland	626.4	1.6	216.3	0.6	410.1	1.1
Portugal	872.5	8.4	232.0	2.2	640.5	6.2
Romania	350.8	1.8	148.4	0.8	202.3	1.0
Slovenia	241.2	11.7	67.0	3.2	174.2	8.4
Slovakia	181.6	3.3	150.5	2.8	31.1	0.6
Finland	329.2	6.0	118.8	2.2	210.4	3.8
Sweden	1 675.1	17.0	529.8	5.4	1 145.3	11.6
United Kingdom	8 698.2	13.3	3 250.6	5.0	5 447.5	8.3
Iceland	41.9	12.6	28.1	8.5	13.7	4.1
Liechtenstein	24.2	64.4	8.2	21.9	16.0	42.5
Norway	774.0	14.9	349.7	6.7	424.3	8.1
Switzerland	2 324.5	27.9	1 393.6	16.7	930.9	11.2

Average 6.8%

Note: the values for the different categories of country of birth may not sum to the totals due to rounding.

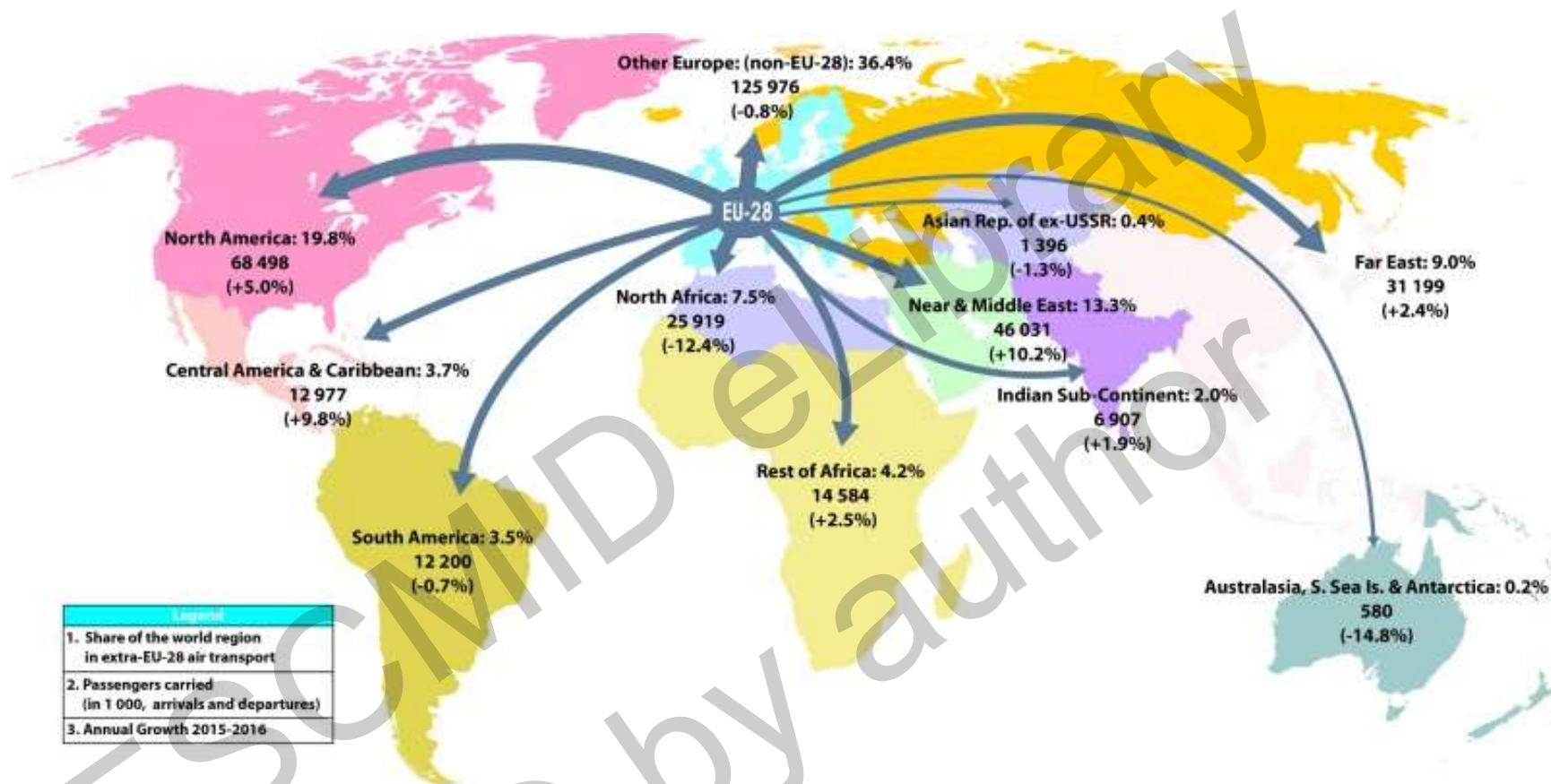
Source: Eurostat (online data code: migr_pop3ctb)

2015-16 Growth in Total Passenger Air Transport by Member State



Source: Eurostat (online data code: avia_paoc)

Extra-EU28-transport.



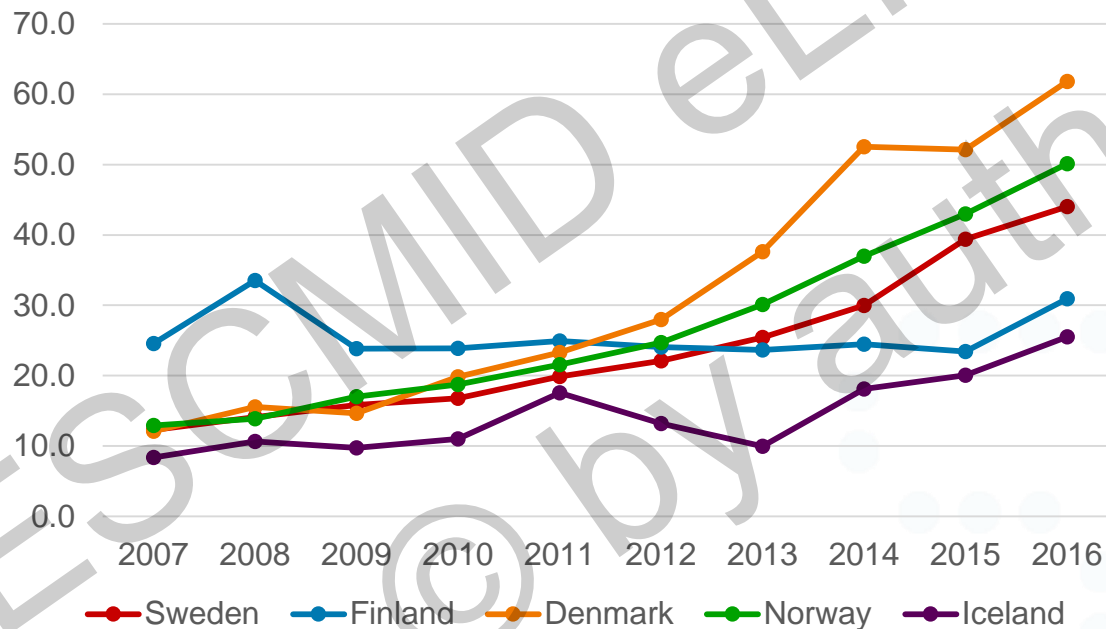
346 mill EU passengers outside EU28 in 2016

-globally 3.7 billion passengers in 2016, *International Air Transport Association (IATA)*

Why are low prevalence countries interesting?

- ❖ Nordic countries: few cases that are all registered (2007-)
- ❖ Denmark as a laboratory for CA-MRSA epidemiology
- ❖ All Danes have a unique social security number

Incidence of new MRSA cases per 100,000 inhabitants, Nordic countries



www.nordicmrsa.org

- ❖ National surveillance of MRSA in Denmark since 1992
 - Notifiable since nov. 2006
 - All **MRSA isolates** from new cases are submitted by the Clinical Microbiological Departments to NRL (Statens Serum Institut)
 - Characterized by **spa typing, AST**

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- National surveillance of MRSA in Denmark
 - Notifiable since nov. 2006
 - All MRSA isolates detected at the Clinical Microbiological Departments are submitted to NRL (Statens Serum Institut)
 - Characterized by *spa* typing, AST
 - Case risk factors based on questionnaires filled in by the treating physicians. Within 6 months:
 - **Hospitalized**, worked in hospitals outside the Nordic countries
 - **Close contacts** (household members) being abroad
 - Returned from abroad with **signs/symptoms of *S. aureus*** infection
 - Stayed in places with **poor hygiene/crowding**: warzones, refugees camps, asylum centers
 - Social security number: Information retrieved about case and parents **place of birth** can be obtained

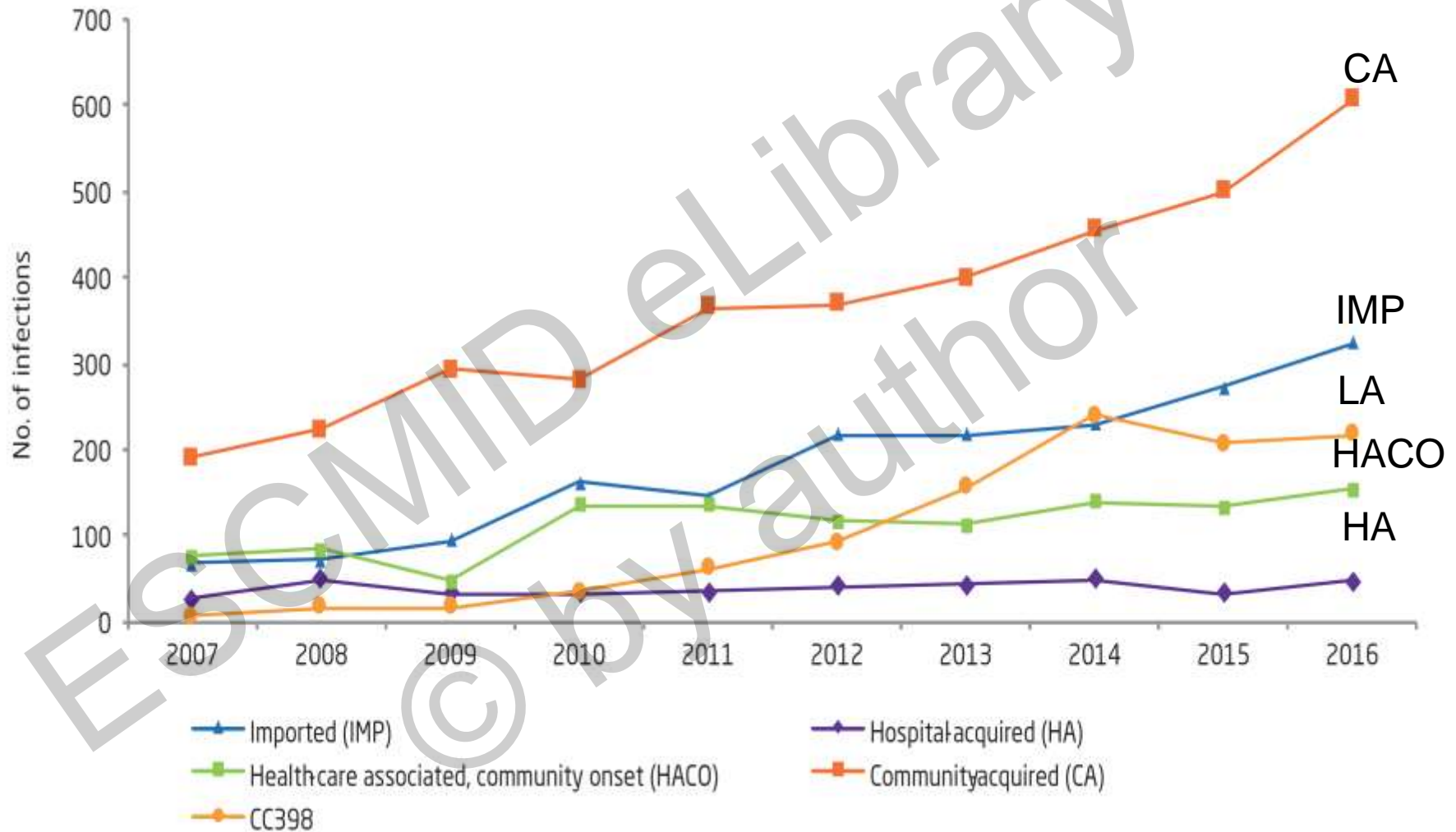
- ❖ How does travel activity and migration affect the MRSA epidemiology in Denmark?
- ❖ Risk assesment
 - Are some travels associated with increased risk of getting MRSA?

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Epidemiological Classification of MRSA Infections

Figure 8.7.2 Number of MRSA infections according to epidemiological classification, Denmark

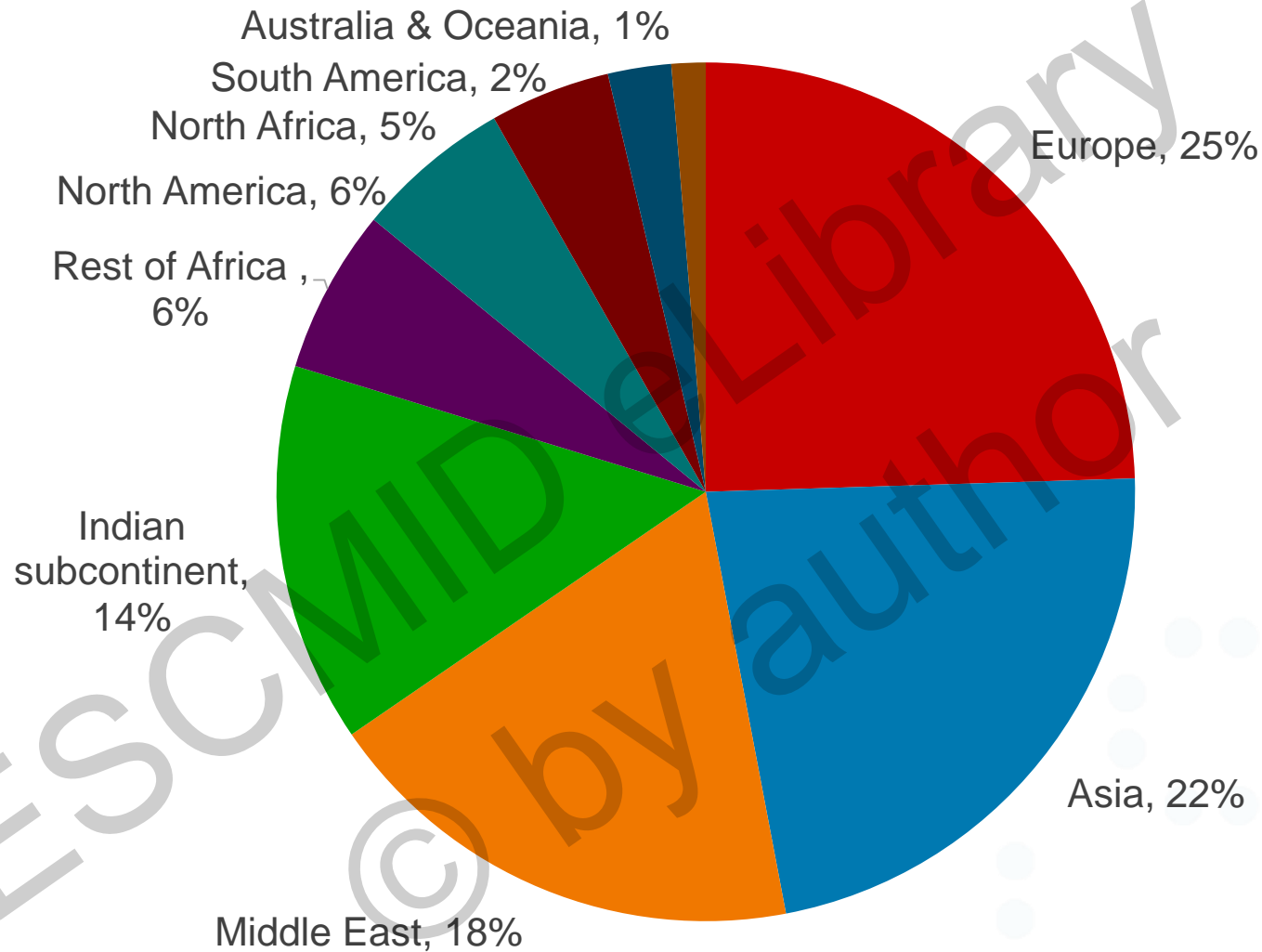
DANMAP 2016



- Imported MRSA cases: N= 3,239, 18% of total cases N=18,012
 - Female: male ratio = 0.88
 - 2249 (69.4%) had **no hospital contact** while abroad registered

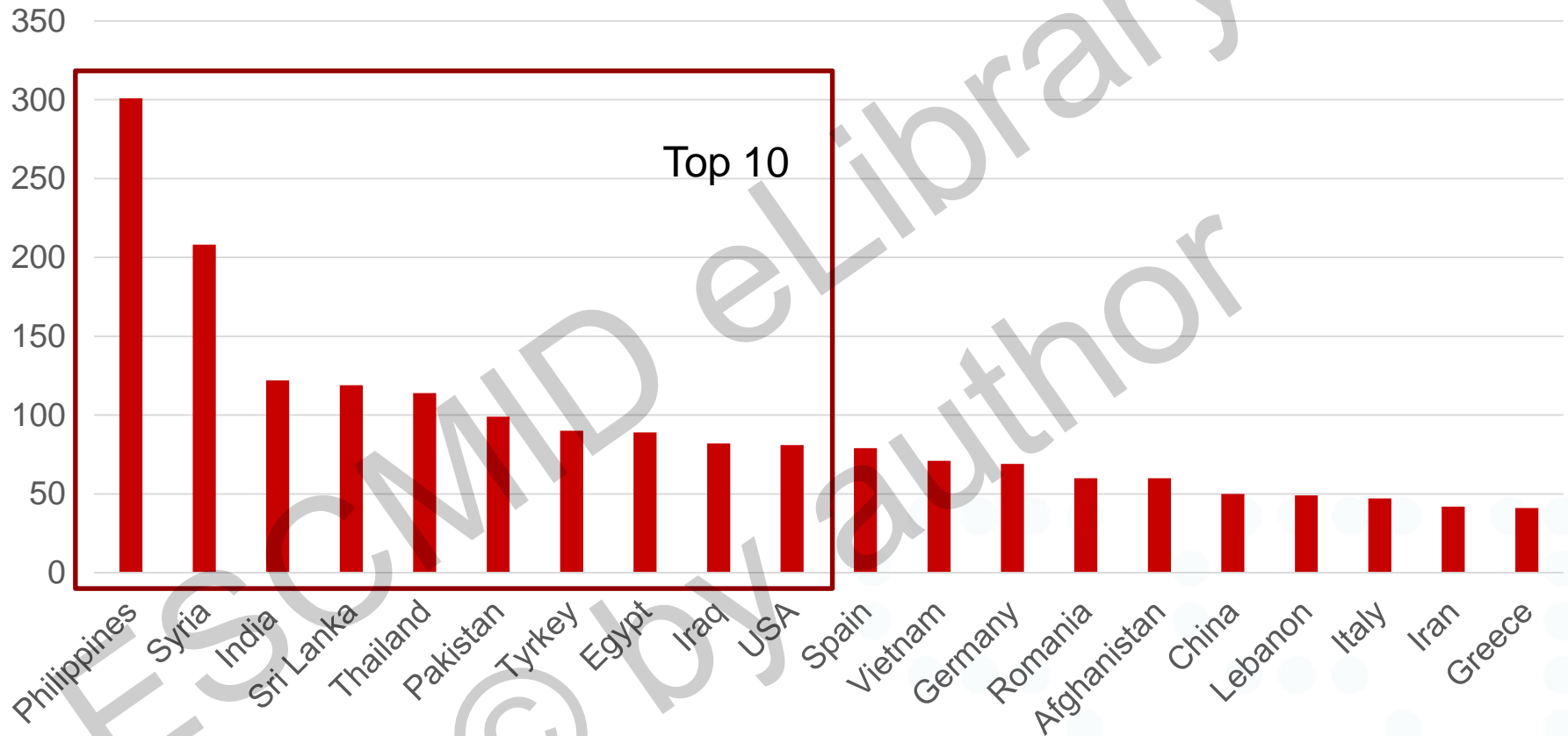
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Countries registered as likely place of acquisition



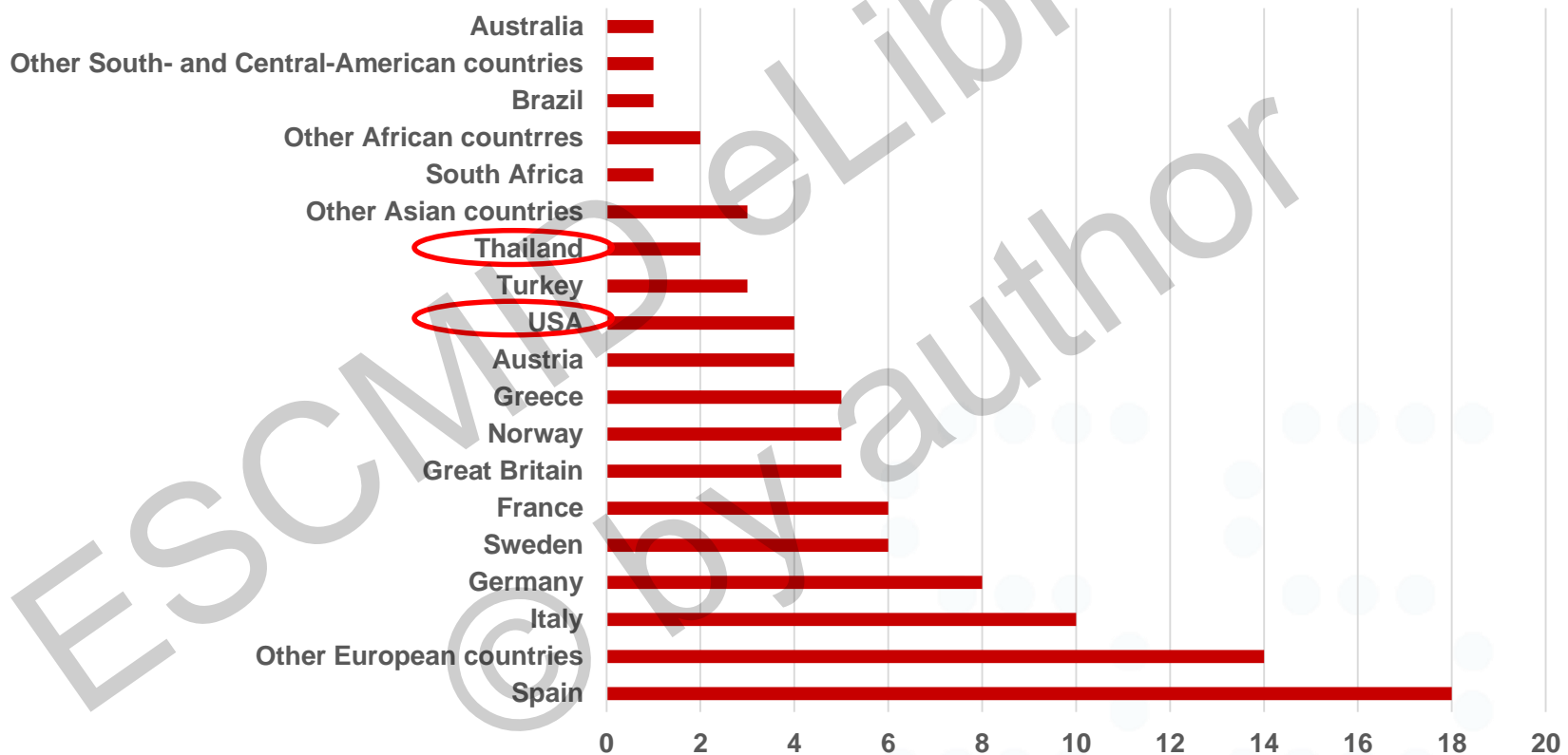
Countries from where MRSA is imported

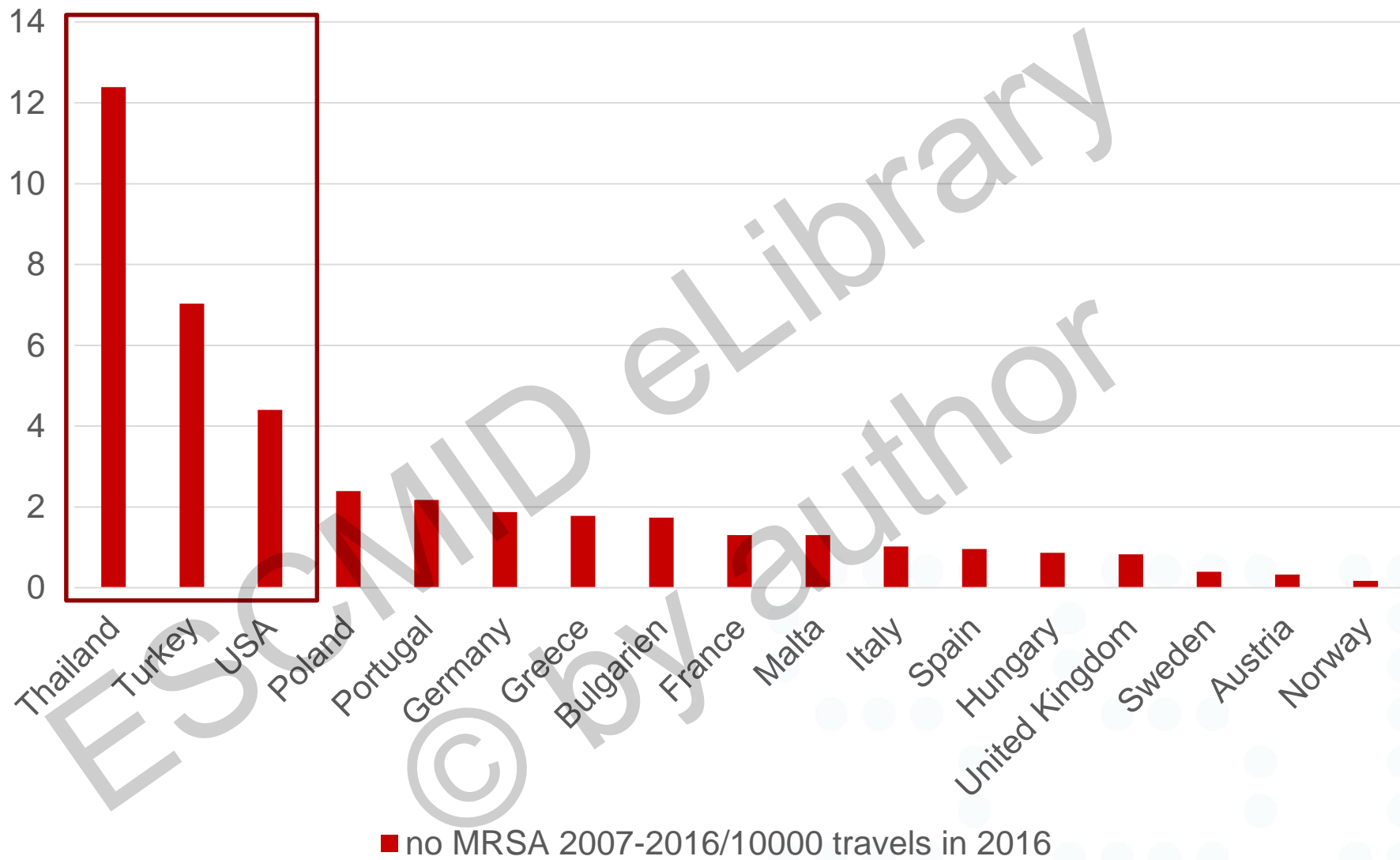
Top 20 countries of imported cases, Denmark 2007-16



- ❖ 81% of all destinations are European countries

Travel destinations for Danish travelers, > 3 nights, 2016 (%)





- ❖ CC annotations were based on *spa* types (94.2%)
 - 26 different clonal complexes (CC)
 - Top 10 CCs accounted for 71.9%

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CC distribution by (sub)continent

CC	Africa N=169	Asia N=619	Australia & Oceania N=35	Europe N=669	Indian subcont. N=390	Middle East N=503	North Africa N=124	North America N=160	South America N=65
CC8 N=400	42 (25)	52(9)	7(20)	97(15)	34(9)	28(6)	15(12)	97(61)	28(43)
CC5 N=392	13(8)	66(11)	4(11)	131(20)	91(23)	42(8)	12(0)	21(13)	12(19)
CC30 N=379	8(5)	257(42)	3(9)	44(7)	18(5)	30(6)	5(4)	2(1.3)	12(19)
CC22 N=328	5(3)	11(2)	1(3)	121(18)	50(13)	118(24)	21(17)	1(0.6)	0
CC1 (N=300)	10(6)	53(9)	3(9)	71(11)	90(23)	41(11)	13(11)	5(3)	0
CC80 N=140	7(4)	4(1)	1(3)	40(6)	6(1.5)	60(12)	18(15)	4(3)	0
CC88 N=119	46 (27)	6 (1)	1(3)	11(1.6)	7(1.8)	38(8)	7(6)	3(1.9)	0
CC6 N=96	3(2)	2 (0.3)	1(3)	16(2)	15(4)	56(11)	2(1.6)	1(0.6)	0
CC59 N=84			1(3)	23(3)	5(1.3)	2(0.4)	1(0.8)	1(0.6)	1(1.5)

CC annotations by country (EUROPE_EUASIA)

CC	Turkey	Spain	Germany	Romania	Italy	Greece	France	Russia	UK
CC5	11 (13)	29 (40)	18 (27)	3 (5)	14 (30)	8 (19)	5 (14)	1 (4)	2 (11)
CC22	22 (25)	14 (19)	25 (38)		6 (13)	2 (5)		20 (80)	8 (44)
CC8	17 (20)	5 (7)	6 (9)	11 (19)	12 (26)	1 (2)	14 (40)	3 (12)	4(22)
CC1	9 (10)	1 (1)	3 (5)	33 (57)	4 (9)	4(9)	1 (3)		1(11)
CC30	3 (3)	4 (5)	3 (5)	1 (2)	1(2)	3 (7)	4 (11)		3 (33)
CC80	9 (10)	1(1)	1 (1)	8 (14)	1(2)	12 (28)	2 (6)		
Others	17 (20)	19 (26)	10 (15)	2 (3)	8(17)	11(26)	9 (26)	1 (4)	

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PVL POSITIVE IMPORTED, CA-MRSA

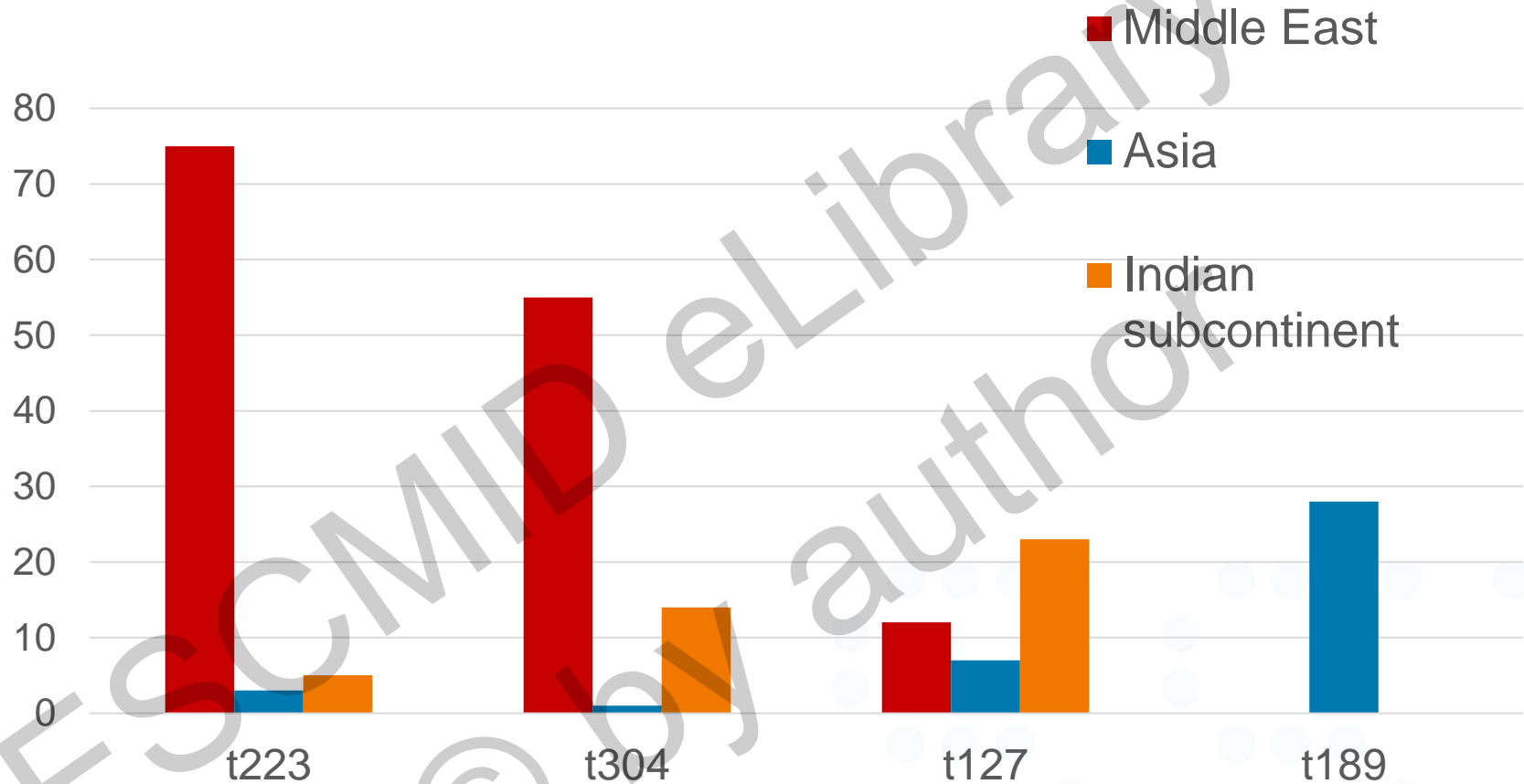
- ❖ 45.3% (1,421/3,136) tested positive for presence of PVL encoding genes
 - 16 CCs, 158 different *spa* types
 - Top 20 *spa* types included 81% of all

Clonal Complex	Number	Predominant <i>spa</i> types
CC30	373	t019 (N=373) South West Pacific CA-MRSA
CC8	252	t008 (N=252) USA300
CC1	178	t657 (N=178) Bengal Bay CA-MRSA
CC80	149	t044 (N=149) European CA-MRSA
CC5	138	t002 (N=113), t105 (N=13)
CC59	74	t437 (N=70), others (N=4)
CC22	68	t005 (N=26), t853 (N=25)
CC88	64	t690 (N=26), t1339 (N=9)

Geographic distribution of imported PVL Positive MRSA cases according to *spa* types

CC-/spa type	Asia	Indian subcontinent	Europe	Middle East	North Africa	Rest of Africa	North America	South America	Australia & Oceania
CC30: t019	199	3	20	4	1	3	-	8	3
CC8: t008	22	12	35	7	4	4	75	21	4
CC5: t002	3	73	18	4	-	1	2	-	1
CC80: t044	1	-	33	47	12	5	2	-	-
CC1: t657	6	62	5	14	-	-	2	-	-
CC59: t437	36	1	16	2	1	-	1	-	1
CC22: t005	2	19		2	2	-		-	-
CC88: t690	-	2	3	14	-	3	-	-	-

PVL negative MRSA

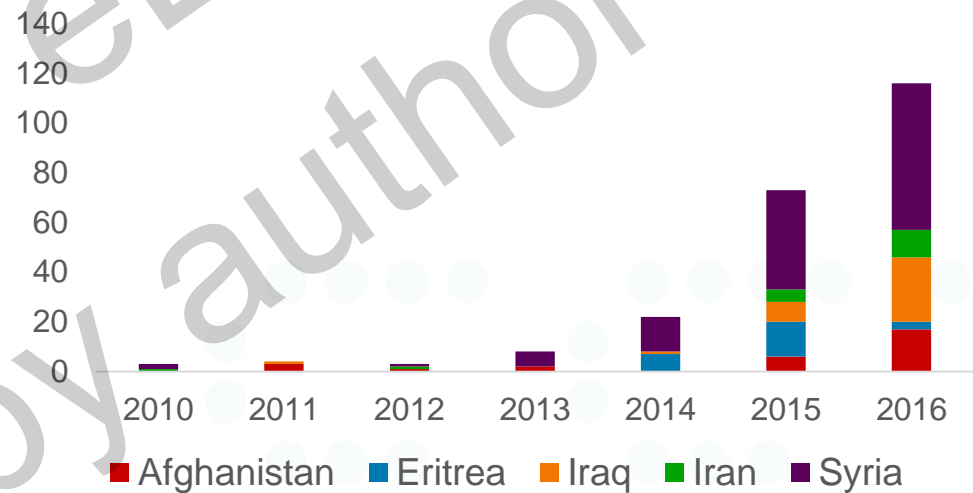


Asylum seekers

- ❖ Asylum seekers: 519 (16%)
- ❖ 40 different countries
- ❖ 119 different *spa* types

Top 5 <i>spa</i> types	No.
t223	105
t304	65
t044	37
t127	24
t002	20

Nationality of MRSA cases staying
in asylum centers



- ❖ Place of birth were available for 2720 cases (with social security number)
 - **40.6%** born and both parents in Denmark
 - **59.4%** born or at least one parent born abroad
- ❖ The proportion of cases born or with parents born outside Denmark was significantly higher among MRSA cases than for the **general population (10.8 %)**
 - 77.9% of persons born outside Denmark acquired MRSA during travel in a country at the same (sub)continent as country of birth

- Overlap between IMP MRSA lineages and what is registered as CA- MRSA cases
 - Indicate spread in the community of IMP-MRSA
 - Exceptions are CC398 and t024
- Person with a non-Danish origin was highly overrepresented 4,647 (46.5%)

Lineage	Total
CC398: t034	1,958
CC5: t002*	660
CC8: t008*	525
CC1: t127*	341
CC398: t011	317
CC6: t304*	298
CC30:t019*	297
CC80: t044*	282
CC22: t223*	211
CC8: t024	208
CC22: t032*	152

- ❖ Import were registered for 18% of all new MRSA cases
- ❖ No european countries among top 10 Countries of import:
predominantly the Philipinnes, Middle East countries, India and USA
 - not among the predominant travel destinations
- ❖ 69% did not report hospital contact
 - Europe 55%, Middle East 83%
 - The predominant MRSA linages were few succesfull (PVL+) CA-MRSA clones
- ❖ 59% of cases were born or had parents born outside Denmark
 - Different travel, with closer contact to family and friends and thereby increased risk of becoming a carrier?
 - Community acquisition seems to be a risk when travelling in some countries

- ❖ USA: 2% estimated as MRSA carriers *www.cdc.gov*
- ❖ China: 2.3% MRSA in CA- infections *Liu Y et al. Emerg Microbes Infect. 2016*
- ❖ India: The nasal carriage of MRSA among outpatients 2.3- 3%. Up to 65% in CA- infections. *Singh et al. J Lab Physicians. 2017 Oct-Dec;9(4):317-321; George K. et al. J Clin Diagn Res. 2016*
- ❖ Middle East:
 - Pilgrims attending Mecca Haji: MRSA carriage rate of 15- 20%. *Johargy A et al. Egypt J Med Microbiol 2011; Dablood A, Open J Saf Sci 2011 and Ahmed B, Asian J Sci Tech 2014*
 - 2-63% of patients with a community onset of infections in 2015. *Leangapichart T et al. Travel Med Infect Dis. 2017*

- ❖ The Danish experience can be extrapolated to other European countries
- ❖ Spread from community to hospitals
- ❖ Screening strategies should be evaluated concordingly
 - Include all admitted persons with a recent history of travel, not only persons who have been hospitalized abroad

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❖ SSI- NRL

- Andreas Petersen
- Jesper Larsen
- Robert Skov
- Technicians

❖ Clinical Microbiological Departments in Denmark

❖ Nordic NRL

- Kjersti Wik Larssen and Frode Gran Wirth (Norway)
- Sara Haeggman (Sweden)
- Laura Lindholm (Finland)
- Gunnstein Aegir Haraldsson

Thank you and questions!

- ❖ Should I Stay Or Should I Go (*The Clash, 1992*)



TRAVEL DATA, TYPE OF TRAVEL >3 DAYS, 2016 (%)

