Cancer Chemotherapy and Travel Related Infectious Diseases

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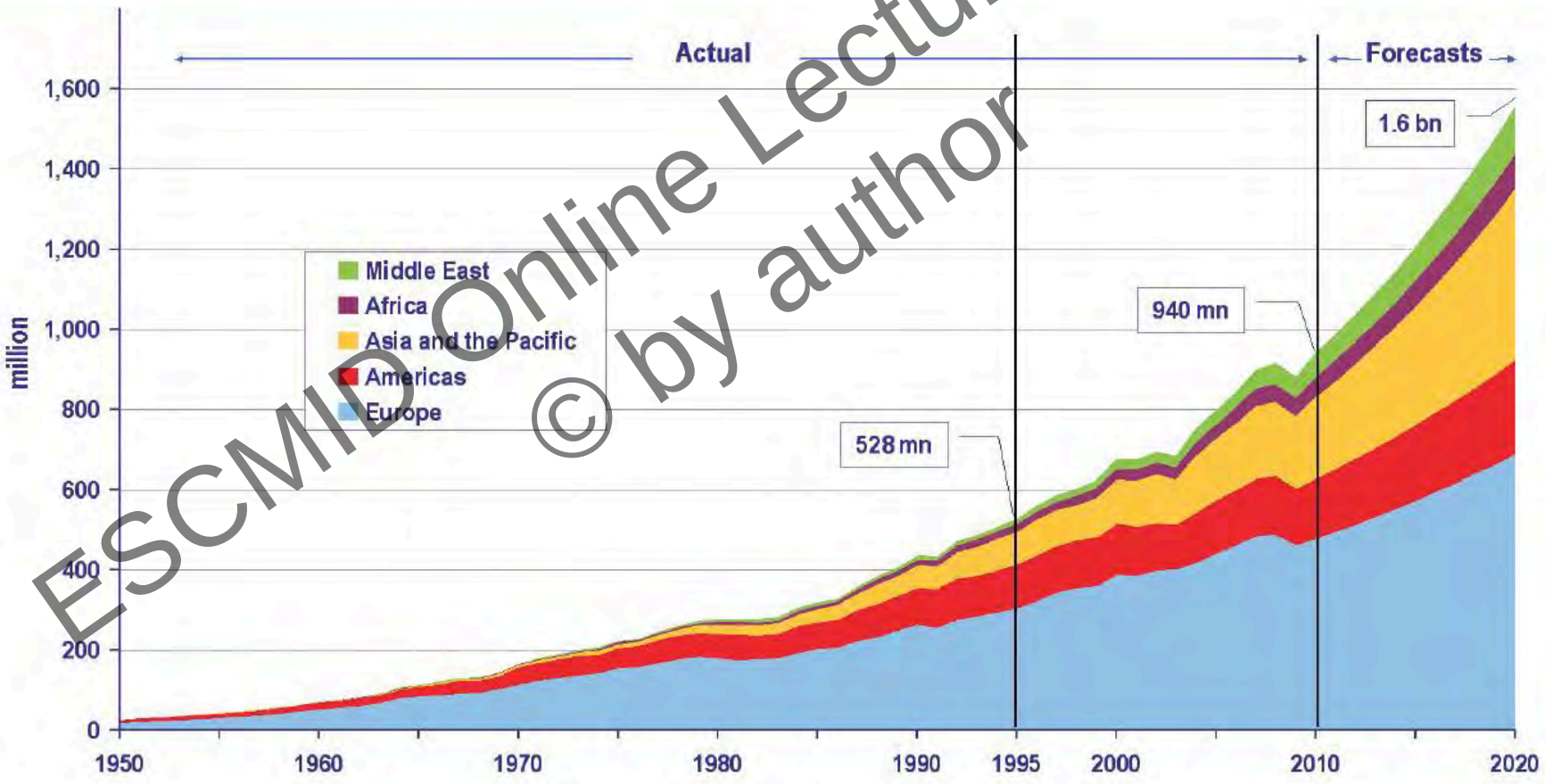
International Tourist Arrivals 1950-2020



WTO 2011. http://mkt.unwto.org/sites/all/files/docpdf/unwtohighlights11enhr_0.pdf

Extend of the Problem…

- 3.6% of the USA population
  - Acquired immunodeficiency due to
    - Organ transplant recipients
    - Patients with HIV infection or
    - Cancer
  - If pregnant women and the elderly are included this proportion will be 20%

Trevejo RT, et al. Vet Res 2005;36:493

Health Risks of Travelers with Medical Conditions

- Retrospective study in a travel clinic in Amsterdam
  - January-October 2010
  - Travelers with underlying immunosuppressive diseases (n=345)
  - Healthy matched control group (n=100)
  - Follow-up by telephone

Wietan RW, et al. J Travel Med 2012;19:104

Travel-Related Diseases in Patients with Underlying Diseases

Table 2 Differences in travel-related disease (TRD) occurrence among travelers with pre-existing conditions, compared to healthy travelers

	N	TRD	Traveled weeks	IRR*
Total underlying medical conditions†	345	99	1148.14	2.16 (1.21–3.86)
Immune suppressants	88	29	291.71	2.49 (1.29–4.79)
1. Prednisolone	15	6	47	3.20 (1.21–8.42)
2. Antimetabolites	18	6	51.43	2.95 (1.12–7.76)
3. Transplant-related drugs	18	9	54.57	4.10 (1.75–9.60)
4. Chemotherapeutic agents	31	6	86.43	1.75 (0.67–4.60)
5. Tumor necrosis factor-alpha blockers	24	6	83.43	1.81 (0.69–4.77)
Gastric barrier reduced†	66	20	188.57	2.65 (1.52–5.33)
Diabetes mellitus	54	13	158.86	2.05 (0.95–4.42)
IDDM	38	10	107.29	2.34 (1.03–5.34)
NIDDM	16	3	51.57	1.45 (0.41–5.08)
HIV	32	12	133.86	2.24 (1.16–4.92)
CD4 <500/μL	19	8	58.86	3.40 (1.40–8.20)
CD4 >500/μL	13	4	75	1.33 (0.43–4.10)
Healthy travelers	100	13	326.14	Reference group

Wietan RW, et al. J Travel Med 2012;19:104

Travel-Related Diseases

Table 4 Specific travel-related diseases (TRDs) in various groups of travelers with underlying medical conditions and healthy travelers

	Immune-suppressants	Age > 60	Gastric barrier reduced	Diabetes mellitus	HIV	Overall underlying conditions	Healthy
N	29	22	20	13	12*	99*	13
GI†: acute diarrhea	18 (62.1)	11 (50.0)	10 (50.0)	6 (46.2)	7 (58.3)	54 (54.5)	6 (46.2)
GI†: chronic diarrhea	3 (10.3)	2 (9.1)	3 (15.0)	1 (7.7)	1 (8.3)	10 (10.1)	1 (7.7)
GI†: other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0)
Fever	4 (13.7)	2 (9.1)	1 (5.0)	2 (15.4)	1 (8.3)	13 (13.1)	0 (0)
Dermatological	1 (3.4)	2 (9.1)	3 (15.0)	1 (7.7)	1 (8.3)	6 (6.1)	3 (23.1)
Respiratory	2 (6.9)	4 (18.2)	2 (10.0)	2 (15.4)	2 (16.6)	9 (9.1)	0 (0)
Other	0 (0.0)	1 (4.5)	1 (5.0)	1 (7.7)	0 (0.0)	5 (5.1)	3 (23.1)

Wietan RW, et al. J Travel Med 2012;19:104

The Effects of Immunosuppressive Agents

- Blockage of clonal expansion
  - Destruction of reacting T and/or B cells
  - Interference with the co-stimulatory signals
  - Blocking the intracellular signal of the antigen-recognizing T-cell receptor
  - Inhibition of DNA synthesis and cell proliferation
- Modulation of the the effector T-cell or B-cell response

Halloran PF. N Engl J Med 2004;351:2715

Results of Immunosuppressive Therapy

- Primary immune response to antigens severely hampered
  - Poor response to vaccines
  - Booster dosages may remain effective
    - Clonal expansion of memory cells is inhibited resulting in lower level of antibody response and shorter duration
  - Live vaccines contraindicated
    - Delayed clearance of replicated virus
    - Increased risk of vaccine-associated disease

Visser LG. Infect Dis Clin N Am 2012;26:609

Cytotoxic Agents

- Cytotoxic to rapidly dividing cells
  - Activated T and B cells
  - Bone marrow, gut epitelium, skin
- Activity of **Azathioprine** can last up to 2 months after stopping therapy
- **Mycophenolic acid** disrupts primary and secondary immune response
  - Highly active yellow fever and dengue virus in vitro
  - Immunosuppressive effect lasts at least 5 days

Visser LG. Infect Dis Clin N Am 2012;26:609

Cytotoxic Agents

- **Methotrexate** (MTX) inhibits purine and thymidine synthesis
  - Induces apoptosis of naïve and memory T cells
- Immunosuppressive effect may last up to 4 weeks
- Absorption from the proximal jejunum and reabsorption from tubuler cells in kidney are variable
  - Impossible to determine a lowest dose, below which, live vaccines can be administered
- MTX can inhibit replication of 17D yellow fever virus at therapeutic concentrations

Visser LG. Infect Dis Clin N Am 2012;26:609

Allogeneic Hematopoietic Stem Cell Transplantation

- Naïve T-cell production (thymopoiesis)
  - In one year in younger persons
  - 2-3 years in adults 20-59 years old
    - Those with GVHD may not recover at all
- Naïve B-cells appear 2 months after tx
  - Total reconstitution after 1-2 years, longer if GVHD occurs
- Revaccination 6 months to 1 year after tx
  - Complete series of childhood vaccines

Visser LG. Infect Dis Clin N Am 2012;26:609

Practical Approach To Travellers with Severe Immunosuppression

- Determine the effect of the underlying malignancy and/or chemotherapy
  - Restore gastric ascidity
- Avoid live-attenuated vaccines
  - Yellow fever vaccine may be protective given during the last 10 years
- If immunosuppressive therapy was stopped, preferably should be restarted 4 weeks after vaccination

Visser LG. Infect Dis Clin N Am 2012;26:609

Practical Approach (contd…)

- Check antibody titers
  - 4-8 weeks after vaccination
  - Booster with inactivated vaccines produces low-level, short duration antibody response
    - Revaccination at shorter intervals
- Give travel health information including
  - Skin care (sun protection)
  - Hand hygiene
  - Early antibiotic tretament of traveller's diarrhea

Visser LG. Infect Dis Clin N Am 2012;26:609

Enteric Infections/Zoonosis and Immunosupression

Infecting pathogen	Disease in immunosuppressed
Salmonella spp.	Increased risk of bacteremia, other complications and mortality
Campylobacter spp.	Recurrent and chronic infections
E. coli O157:H7	Increased risk of infection
Y. enterocolitica	Increased risk of bacteremia
L. monocytogenes	Severe infection, meningitis

Trevejo RT, et al. Vet Res 2005;36:493

Other Pathogens Causing Zoonotic Infections in the Imunosuppressed

- **Respiratory pathogens**
  - ***Bordetella bronchoseptica***
  - ***M. tuberculosis* and non-tuberculous mycobacteria**
  - ***Rhodococcus equi***
- **Vector borne diseases**
  - ***Bartonella hanselae***
- **Animal bites and scratches**
  - ***Captocytophaga canimorsus***
  - ***Pasteurella multocida***

Trevejo RT, et al. Vet Res 2005;36:493

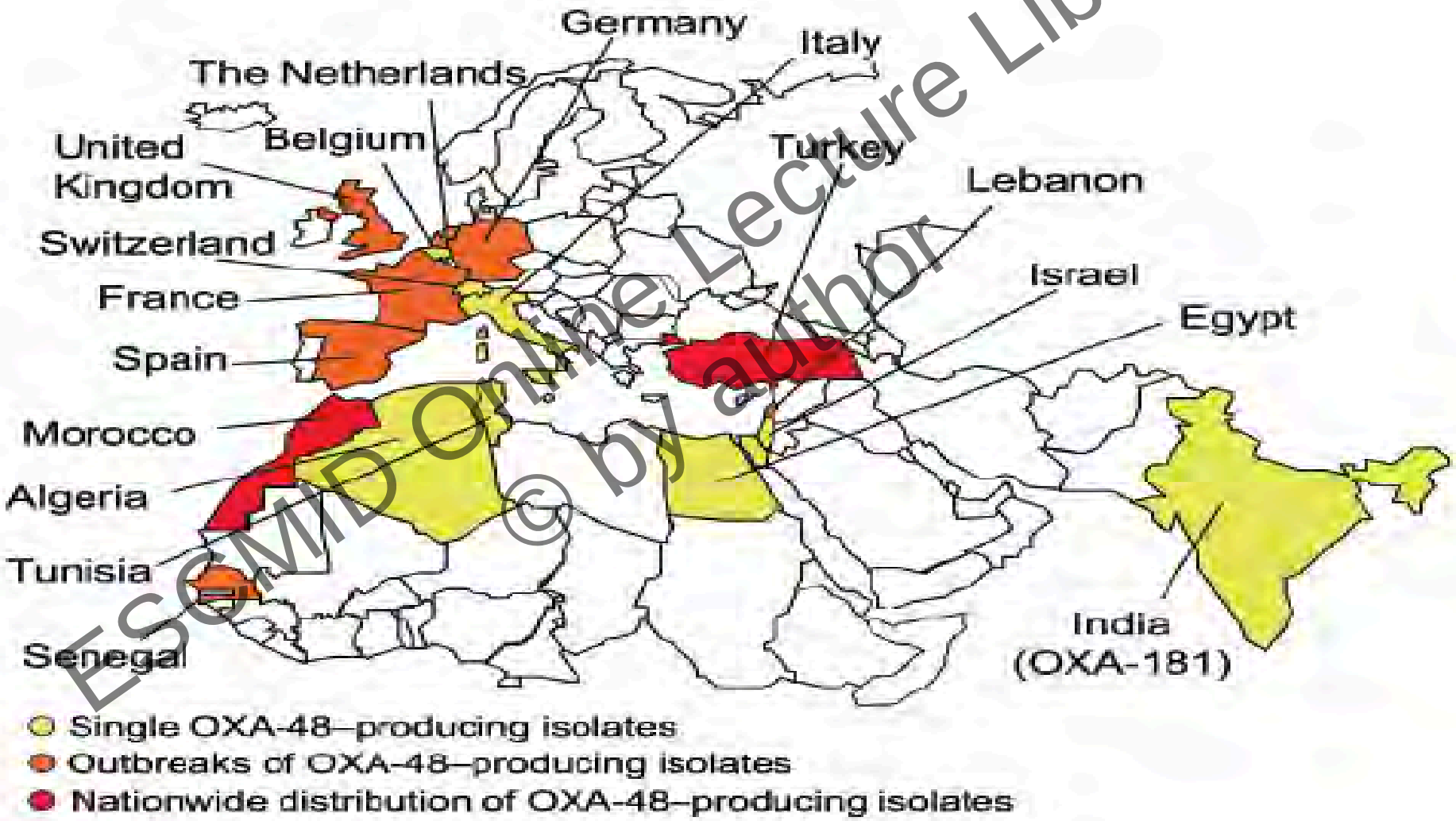
CTX-M Extended-spectrum β-lactamases Worldwide

Hawkey & Jones. J Antimicrob Chemother 2009;64 (Suppl 1):i3

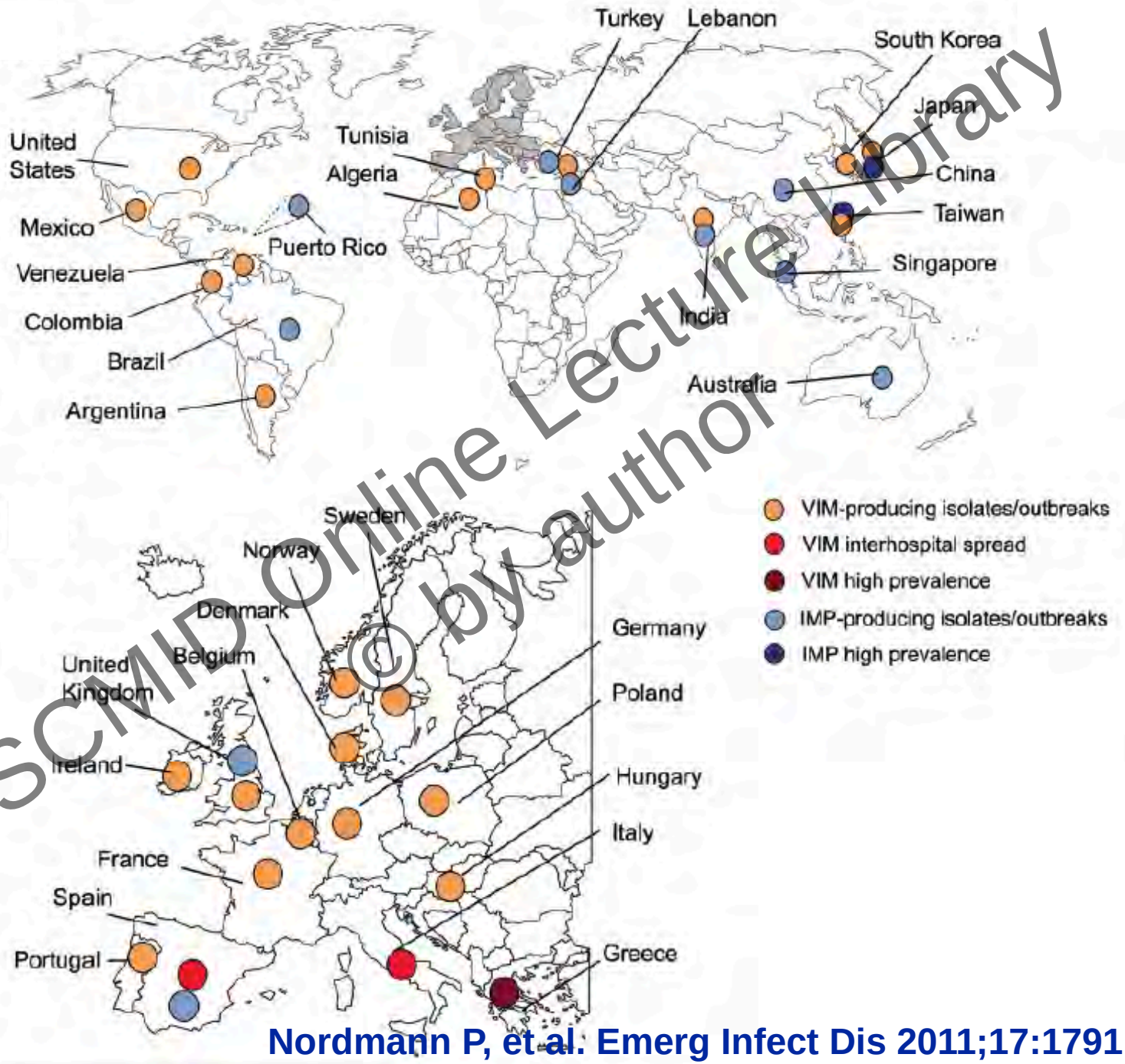
Emerging Carbapenemases in Enterobacteriaceae

Courtesy of DM Livermore

Geographic Distribution of OXA-48 Producers

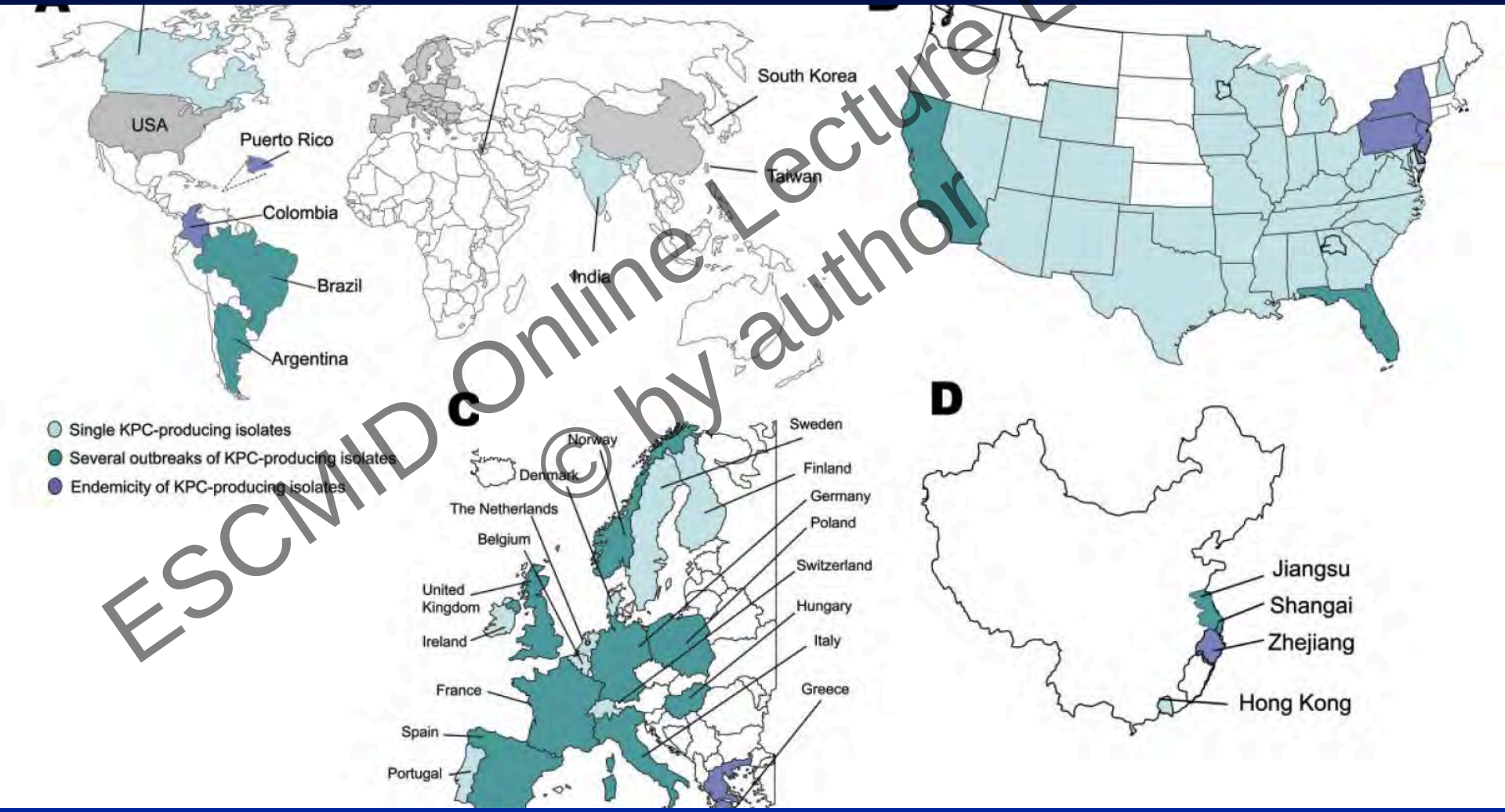


Nordmann P, et al. Emerg Infect Dis 2011;17:1791



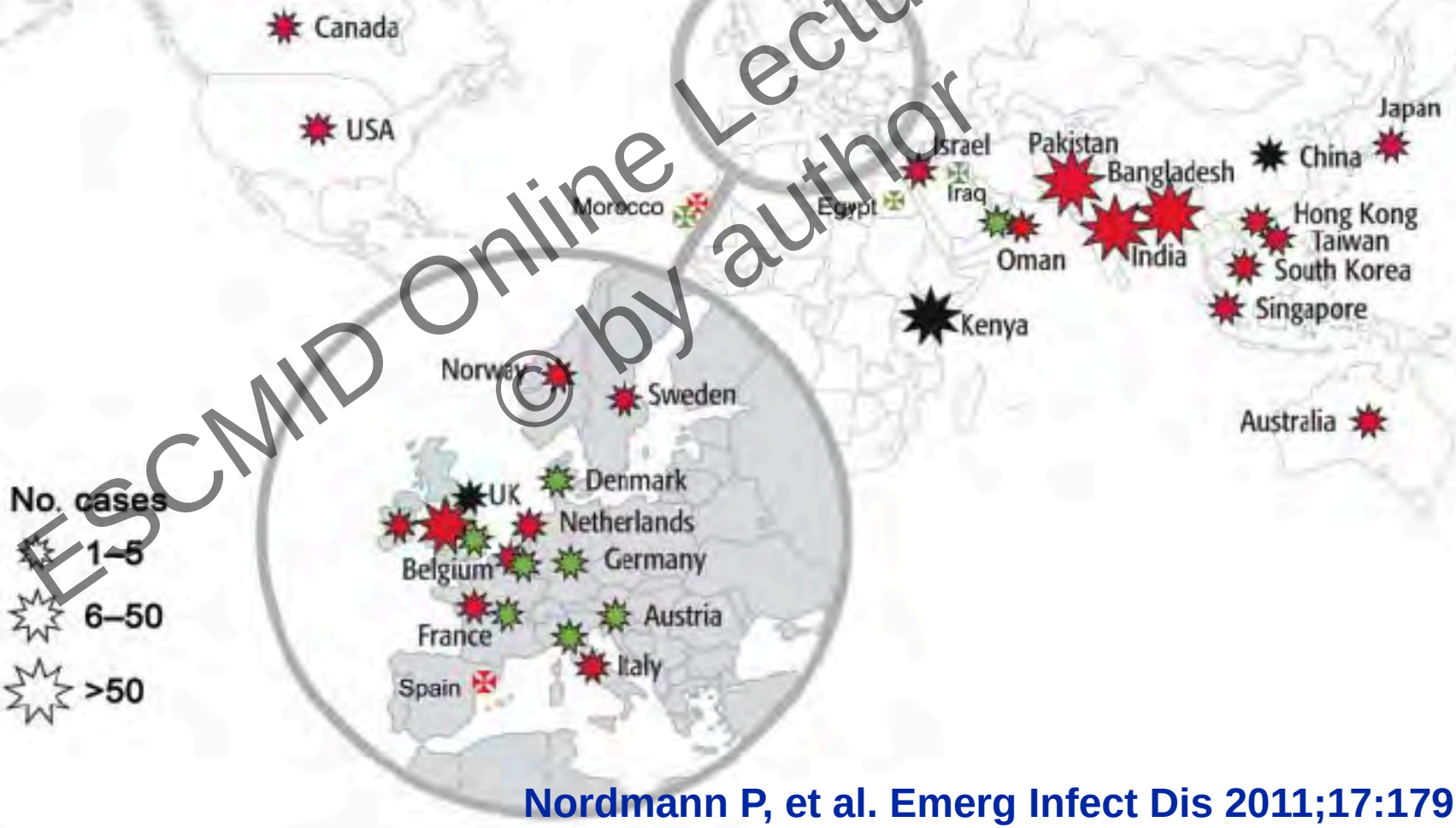
Nordmann P, et al. Emerg Infect Dis 2011;17:1791

Global Distribution of KPC Producers



Nordmann P, et al. Emerg Infect Dis 2011;17:1791

Geographic Distribution of NDM-1 Producers



Nordmann P, et al. Emerg Infect Dis 2011;17:1791

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Summary

Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi

Methods Swabs absorbing about 100 µL of seepage water (ie, water pools in streets or rivulets) and 15 mL samples of

Lancet Infect Dis 2011; 11:355–62

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- Tap water and seepage samples within a 12 km radius of New Delhi between Sept 26 to Oct 10, 2010
- Bacteria with bla_{NDM-1} detected in
  - 2/50 tap water
  - 12/171 seepage samples
- 20 strains were found
  - 11 spp. in which NDM-1 not described before
  - Plasmid transfer more efficient at 30°C than 25°C or 37°C

Walsh T, et al. Lancet Infect Dis 2011;11:355

	Species	Minimal inhibitory concentration (mg/L)												Typical bla_{NDM-1} antibiogram	Genetic location	Plasmid		
		CTX	CTZ	IMP	MER	ATM	GEN	AMI	TOB	CIP	FOS	TIG	COL			Size	Stability*	Type
From waste seepage																		
B-3-2	*Pseudomonas putida*	64	4	0·5	2	64	0·25	1	0·25	0·125	256	4	0·125	No	Plasmid	ND	No	–
1-19	*Pseudomonas pseudoalcaligenes*	64	64	2	4	32	2	1	4	16	16	2	0·25	No	Plasmid	ND	No	–
3-1	*Escherichia coli*	512	256	16	32	64	8	4	16	32	16	4	0·5	Yes	Plasmid	140 kb	Yes	A/C
21-9	*Pseudomonas oryzihabitans*	16	4	2	2	16	0·25	2	0·25	0·25	4	4	0·25	No	Plasmid	ND	No	–
25-4	*Klebsiella pneumoniae*	512	256	32	128	64	32	64	16	32	256	8	0·25	Yes	Plasmid	140 kb	Yes	–
33-5	*Escherichia coli*	256	256	64	64	64	16	32	64	32	2	0·5	0·125	Yes	Plasmid	140 kb	Yes	A/C
65-4	*Escherichia coli*	256	128	8	64	32	16	2	32	16	16	0·5	0·125	Yes	Plasmid	140 kb	Yes	–
65-5	*Shigella boydii*	512	512	4	16	256	32	16	8	64	2	4	1	Yes	Plasmid	250 kb	Yes	–
72-28	*Sutonella indologenes*	32	4	2	4	32	1	2	0·5	0·25	>1024	8	2	No	Plasmid	..	No	–
79-6	*Pseudomonas pseudoalcaligenes*	128	16	2	4	32	4	2	2	8	16	8	0·25	No	Plasmid	280 kb	Yes	–
107-5	*Aeromonas caviae*	64	32	16	8	8	8	2	8	16	128	8	0·25	Yes	Chromo	..	Yes	–
107-7	*Pseudomonas putida*	64	1	32	4	0·25	16	16	32	16	256	16	0·25	No	Plasmid	250 kb	Yes	–
116-4	*Stenotrophomonas maltophilia*	256	256	128	64	64	32	64	16	64	256	16	0·5	Yes	Plasmid	250 kb	Yes	–
116-14	*Vibrio cholerae*	>256	>256	8	8	2	1	8	2	2	64	0·5	8	Yes	Plasmid and chromo	400 kb	Yes	–
116-17	*Vibrio cholerae*	>256	>256	16	1	2	1	0·5	2	2	64	0·5	8	Yes	Plasmid	170 kb	Yes	A/C
117-4	*Citrobacter freundii*	128	128	64	128	64	32	64	32	32	4	2	0·5	Yes	Plasmid	140 kb	Yes	A/C
From tap water																		
W32-17	*Achromobacter* spp	256	256	4	4	64	32	16	32	32	32	0·5	0·125	No	Plasmid	ND	No	..
W38-14	*Kingella denitrificans*	32	32	4	16	8	8	2	1	4	4	1	0·5	No	Plasmid	ND	No	..
W38-16	*Achromobacter* spp	128	128	4	2	32	32	16	4	16	32	0·5	0·25	No	Plasmid	ND	No	..
W38-17	*Pseudomonas aeruginosa*	256	256	32	32	16	32	64	32	16	256	8	0·5	Yes	Plasmid	ND	No	..

CTX=cefotaxime. CTZ=ceftazidime. IMP=imipenem. MER=meropenem. ATM=aztreonam. GEN=gentamicin. AMI=amikacin. TOB=tobramycin. CIP=ciprofloxacin. FOS=fosfomycin. TIG=tigecycline. COL=colistin. ND=not determined. Chromo=chromosome. *Plasmids were deemed unstable if lost within a 48-h period during subculturing without antibiotic selection.

Table 1: Minimal inhibitory concentration of antimicrobials and genetic characteristics of NDM-1-positive bacteria

Walsh T, et al. Lancet Infect Dis 2011;11:355

The perils of medical tourism: NDM-1-positive *Escherichia coli* causing febrile neutropenia in a medical tourist

Chan H L E, Poon L M, Chan S G, Teo J W P

Case Report

NDM-1 polymicrobial infections including *Vibrio cholerae*

Elizabeth Darley, Janis Weeks, Lim Jones, Victoria Daniels, Mandy Wootton, Alasdair MacGowan, Timothy Walsh

Lancet 2012; 380: 1358

Medical Microbiology, North Bristol NHS Trust, Bristol, UK

In April, 2011, a 49-year-old British man was admitted to our hospital directly from a flight home from India. He presented with extensive electrical burns on his face,

the rest were unknown. The data suggested no evidence of in-vivo transfer of the *NDM-1* gene between strains. His condition deteriorated, and he had pyrexia. Over the

Summary

- Most anticancer drugs block T and/or B cell clonal expansion
- Age-related factors may augment this problem
- Immune reconstitution takes time after chemotherapy and HSCT
- Colonization and/or infection with MDR pathogens may have significant consequences
- These factors should be taken into account while protection formulated for immunosuppressed travelers

Thank you…