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Transmission of *Clostridium difficile* infections in Belgian hospitals

Séminaire
« diagnostic et surveillance des maladies Infectieuses»,
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Outline

Background

Objectives

Methods

Results

Discussion

Conclusion & recommendations

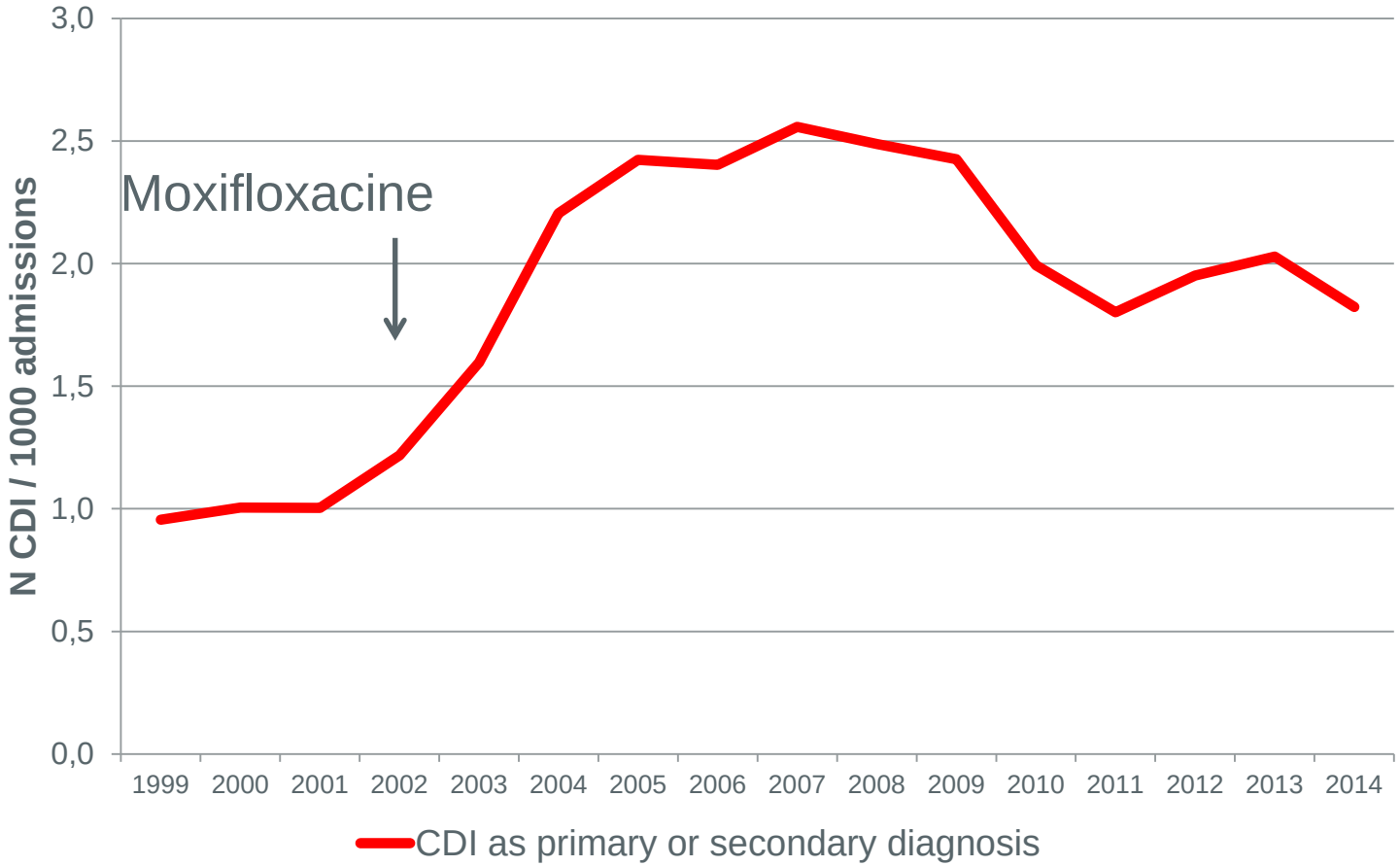
BACKGROUND

Picture courtesy of Johan Vanbroeck, NRC

C. difficile infections

- Major cause of diarrhea and pseudomembranous colitis in hospitals

C. difficile infections recorded in Belgian hospitals, 1999-2014



So: RHM/MKG. Stays with code ICD-9-CM 008.45

C. difficile infections

- Increase observed in several countries

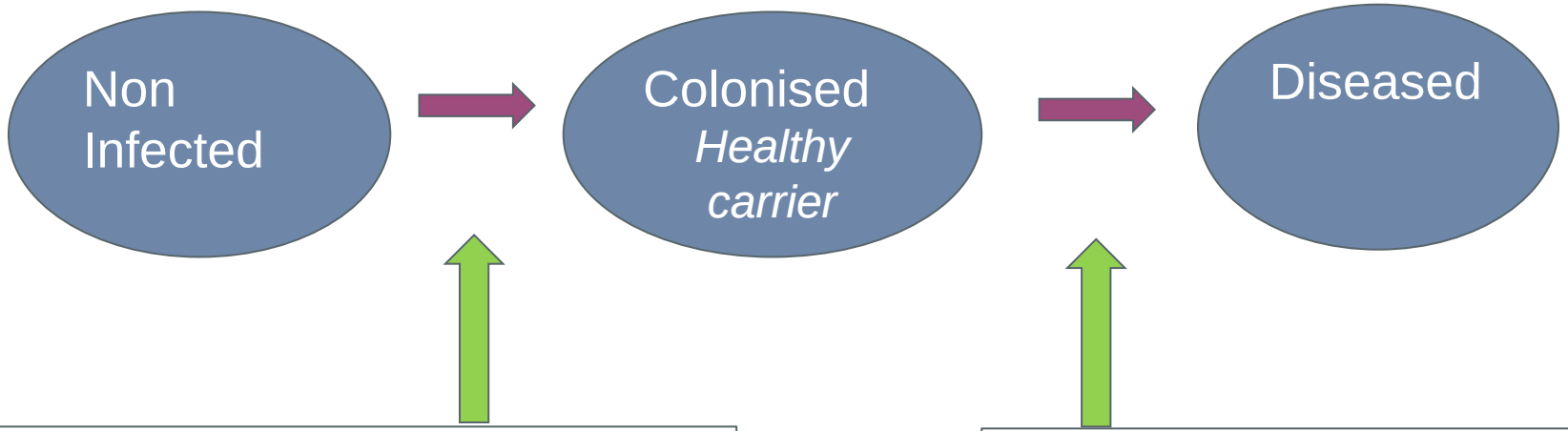
- Most common source of healthcare associated infections in US hospitals
  - *So: Lessa, NEJM, 2015*

C. difficile infections

- +/- 4000 episodes / year in Belgian hospitals (*so: RHM/MKG*)

- Case-based surveillance in Belgian hospitals since 2006
  - Median age: 80 y.o
  - +/- 60% hospital-associated (HA) CDI
    - HA CDI: onset 2 days or more after admission

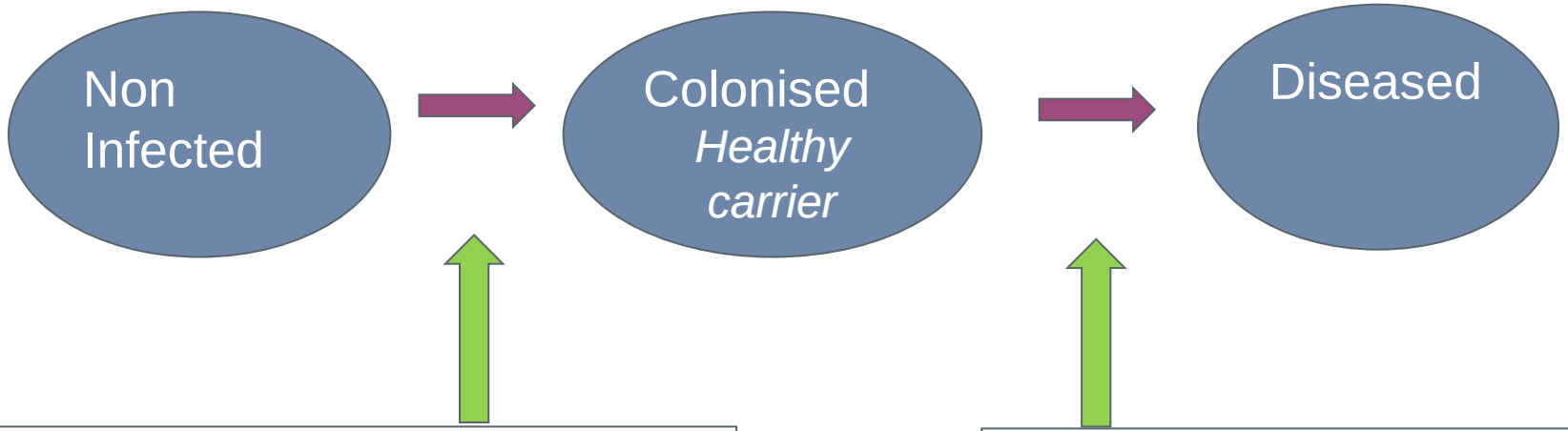
C. difficile infections: (simplified) transmission model



Risk factors for exposure
Hospital
Symptomatic vs asymptomatic patients
Environment?

Risk factors for disease
Disturbance of intestinal flora
Antibiotics, PPI
Elderly patients
…

C. difficile infections: prevention strategies



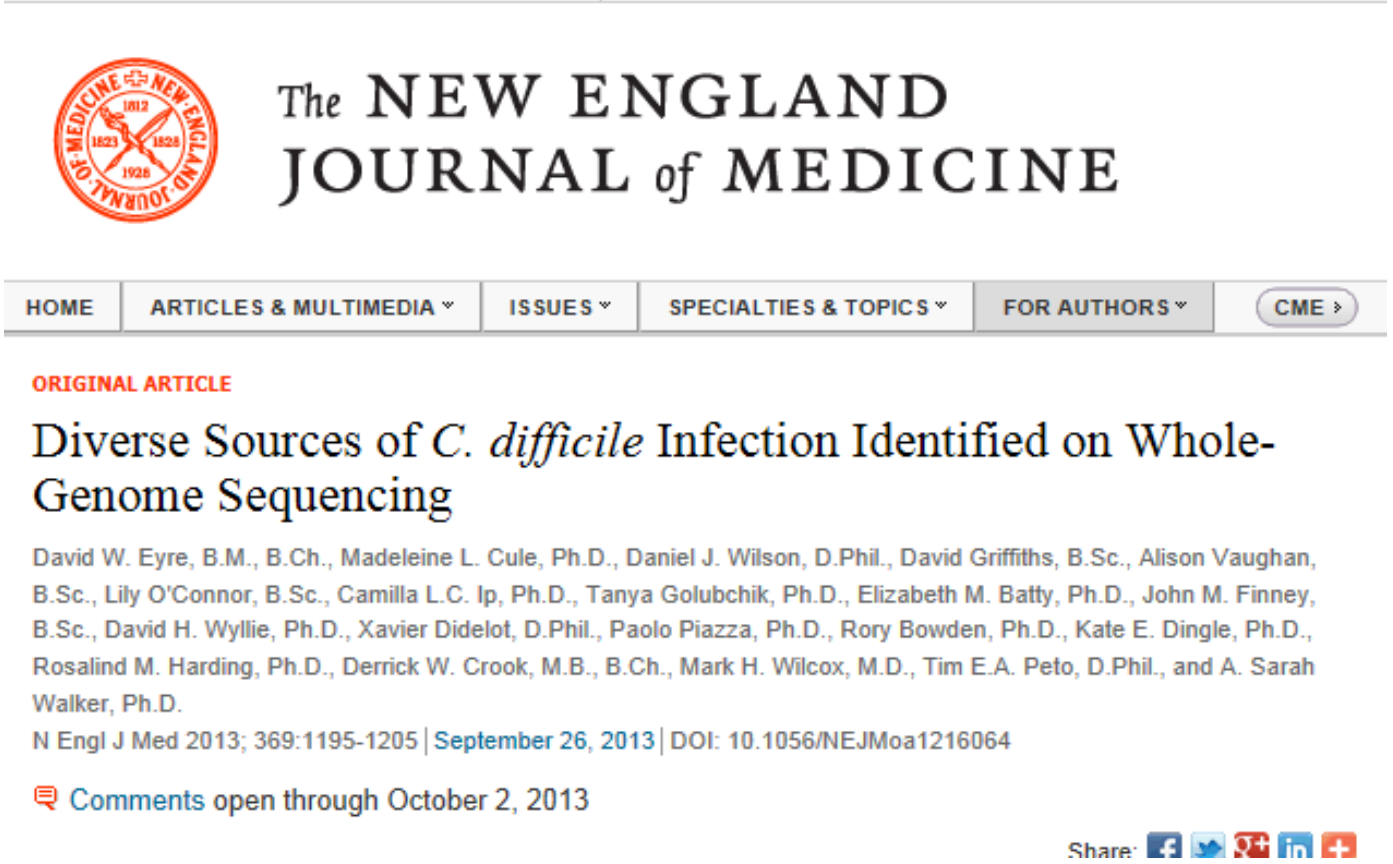
Preventing exposure
Preventing transmission in hospital
Symptomatic
(*asymptomatic patients)*

Preventing disease
Antimicrobial stewardship
…

C. difficile infections

- Until recently, main pathway thought to be case-to-case transmission inside hospitals
- Outbreaks

C. difficile infections: changing epidemiology



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ORIGINAL ARTICLE

Diverse Sources of *C. difficile* Infection Identified on Whole-Genome Sequencing

David W. Eyre, B.M., B.Ch., Madeleine L. Cule, Ph.D., Daniel J. Wilson, D.Phil., David Griffiths, B.Sc., Alison Vaughan, B.Sc., Lily O'Connor, B.Sc., Camilla L.C. Ip, Ph.D., Tanya Golubchik, Ph.D., Elizabeth M. Batty, Ph.D., John M. Finney, B.Sc., David H. Wyllie, Ph.D., Xavier Didelot, D.Phil., Paolo Piazza, Ph.D., Rory Bowden, Ph.D., Kate E. Dingle, Ph.D., Rosalind M. Harding, Ph.D., Derrick W. Crook, M.B., B.Ch., Mark H. Wilcox, M.D., Tim E.A. Peto, D.Phil., and A. Sarah Walker, Ph.D.

N Engl J Med 2013; 369:1195-1205 | September 26, 2013 | DOI: 10.1056/NEJMoa1216064

Comments open through October 2, 2013

Share:

OBJECTIVES AND METHODS

Transmission of *CDI* in Belgian hospitals: objective of the study

- to measure the proportion of hospital-associated CDI (HA CDI) that results from case-to-case transmission within the same hospital

  HA CDI: onset of diarrhea 2 days or more after admission

  - ... in order to orient prevention strategies

- Complete study protocol: http://www.nsih.be/download/CDIF/CDIF_transmission_study_protocol_v7.pdf).

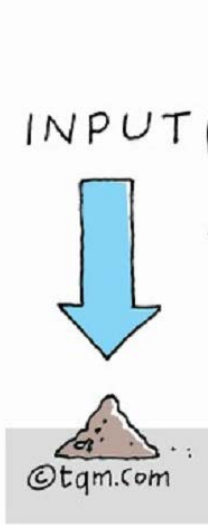
Methods (1) data collection

Study based on data arising from the existing national surveillance

Hospitals (voluntarily) participating in the study

- Register all CDI episodes from Jan 2015 to Jan 2016

- Send *all* strains for typing *to National Reference Laboratory* (NRC)



Methods (2) typing in NRC

- 2-steps typing:

1) Ribotyping (categorical) : all strains

2) Multilocus variant analyses (MLVA) to differentiate between similar ribotypes

C difficile typing: MLVA

- MLVA: continuous grading of relatedness of isolates
- 7 loci
- Comparing isolates: absolute differences in copy numbers at each locus

  (Summed Tandem Repeat Differences, STRD)

  - ”Similar” profile: STRD 0-3
  - ”Different” profile: STRD >=10
  - Undetermined: STRD 4-9

Methods (3) HA- CDI: ascertainment of case-to-case transmission in same hospital

Case-to-case transmission	Criteria
Excluded	**NO** strain with identical ribotype isolated from an earlier* case in the same hospital. OR Strain(s) with identical ribotype identified, but **NO** similar MLVA profile isolated from an earlier* case in same hospital.

* *Earlier: 30 vs 60 days*

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Confirmed	**At least one strain** with *identical* ribotype AND *similar* MLVA profile isolated from an earlier* case in same hospital.

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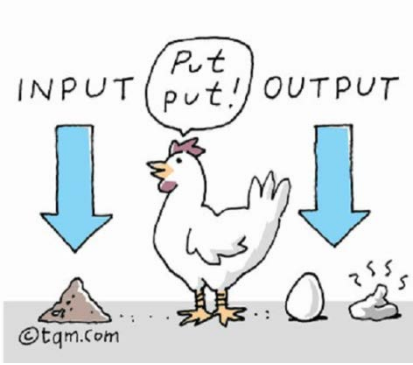
Confirmed	**At least one strain** with *identical* ribotype AND *similar* MLVA profile isolated from an earlier* case in same hospital.
Undetermined	same ribotype isolated from an earlier case*, but similarity of strains (using MLVA) undetermined

* *Earlier: 30 vs 60 days*



RESULTS (PRELIMINARY)

Transmission of *CDI* in Belgian hospitals: Preliminary results (1)

- 25 hospitals with less than 30% missing data

- 1131 CDI episodes reported in surveillance system between Januray 2015- and January 2016
  - 641/1131 (57%) HA CDI

  - 120/1131 (11%) missing ribotyping data

  - 1011 isolates, 143 different ribotypes, 68 isolated once

Transmission of *CDI* in Belgian hospitals: Preliminary results (2)

641 HA-CDI episodes registered

- exclusion
  - No ribotyping data
  - Relapses
  - Episodes occurring during run-in period (30 /60 days)

Evaluated for case-to-case transmission:

- 488 (30 days run-in)
- 429 (60 days run-in)

Preliminary results (3)

HA-CDI evaluated for case-to-case transmission, criteria: 30 days. N=488

step 1: based on ribotyping results	**488**	**100%**
Case-to-case transmission excluded (CCE) (*no identical ribotype isolated in same hospital within previous 30 days*)	351	72%
Case-to-case transmission possible	137	28%

Preliminary results (3)

HA-CDI evaluated for case-to-case transmission, criteria: 30 days. N=488

step 1: based on ribotyping results	**488**	**100%**
Case-to-case transmission excluded (CCE) (*no identical ribotype isolated in same hospital within previous 30 days*)	351	72%
Case-to-case transmission possible	137	28%
step 2: based on MLVA results	**137**	**100%**
CCE	67	49%
Case-to-case transmission confirmed (CCC)	56	41%
Case-to-case transmission undetermined CCU	9	7%
Missing	5	4%

Preliminary results (4)

HA-CDI evaluated for case-to-case transmission

N= 25 hospitals

Time frame	30 days	
Total HA-CDI assessed	488	100%
case-to-case excluded	418	86%
case-to-case confirmed	56	11%
Case-to-case undetermined	9	2%
Missing MLVA data	5	1%

Preliminary results (4)

HA-CDI evaluated for case-to-case transmission

N= 25 hospitals

Time frame	30 days		60 days	
Total HA-CDI assessed	488	100%	429	100%
case-to-case excluded	418	86%	327	76%
case-to-case confirmed	56	11%	59	14%
Case-to-case undetermined	9	2%	10	2%
Missing MLVA data	5	1%	33	8%

Preliminary results (4)

HA-CDI evaluated for case-to-case transmission

N= 25 hospitals

	Median	Min	Max
Total HA-CDI evaluated	15	2	73
Case-to-case transmission confirmed (30 days)	1	0	15
% case-to-case transmission confirmed	7%	0	28%

Transmission confirmed: Clusters size, per ribotype

ribotype	hosp_code	CCC30
27	X	7
32	Y	7
290	X	5
16a	Z	4
16	Y	3

Diversity of MLVA profile, per ribotype

Number of different profiles, for each of 7 loci

Ribotype	N isolates	A6
16	74	26
32	43	15
16a	42	18
27	32	6
3	22	x
5a	14	x

Diversity of MLVA profile, per ribotype

Number of different profiles, for each of 7 loci

Ribotype	N	A6	G8	B7
16	74	26	10	18
32	43	15	6	16
16a	42	18	7	15
27	32	6	4	4
3	22	x	x	x
5a	14	x	x	x

Diversity of MLVA profile, per ribotype

Number of different profiles, for each of 7 loci

Ribotype	N	A6	G8	B7	C6	E7	CD105	CDR60
16	74	26	10	18	30	5	1	11
32	43	15	6	16	19	5	1	2
16a	42	18	7	15	20	3	1	4
27	32	6	4	4	8	2	1	2
3	22	x	x	x	15	3	1	1
5a	14	x	x	x	8	2	1	1

Diversity of MLVA profile, per ribotype

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Ribotype	N	A6	G8	B7	C6	E7	CD105	CDR60
16	74	26	10	18	30	5	1	11
32	43	15	6	16	19	5	1	2
16a	42	18	7	15	20	3	1	4
27	32	6	4	4	8	2	1	2
3	22	x	x	x	15	3	1	1
5a	14	x	x	x	8	2	1	1
12a	4	x	x	x	x	2	1	1

DISCUSSION AND CONCLUSION

Transmission of *CDI* in Belgian hospitals: key finding (1)

- In Belgium, the majority of hospital-associated CDI are NOT genetically related to another symptomatic CDI inside the hospital

- This varies between hospitals

- … sporadic outbreaks occurr

Transmission of *CDI* in Belgian hospitals: key finding (2)

- High diversity of ribotypes
- High diversity of MLVA profiles within ribotypes,
  (With some exceptions!)

Suggests diversity in sources of transmission

Transmission of *CDI* in Belgian hospitals: limitations (2)

- 11% of episodes not typed
  - ➔ could not be evaluated in chain of transmission

- Assumption : genetically related CDI episodes in same hospital are due to direct case-to-case transmission

  … but 2 genetically related episodes might have a common (unidentified) non-case source

Transmission of *CDI* in Belgian hospitals: next step:

- More advanced statistical modelling taking into account missing data

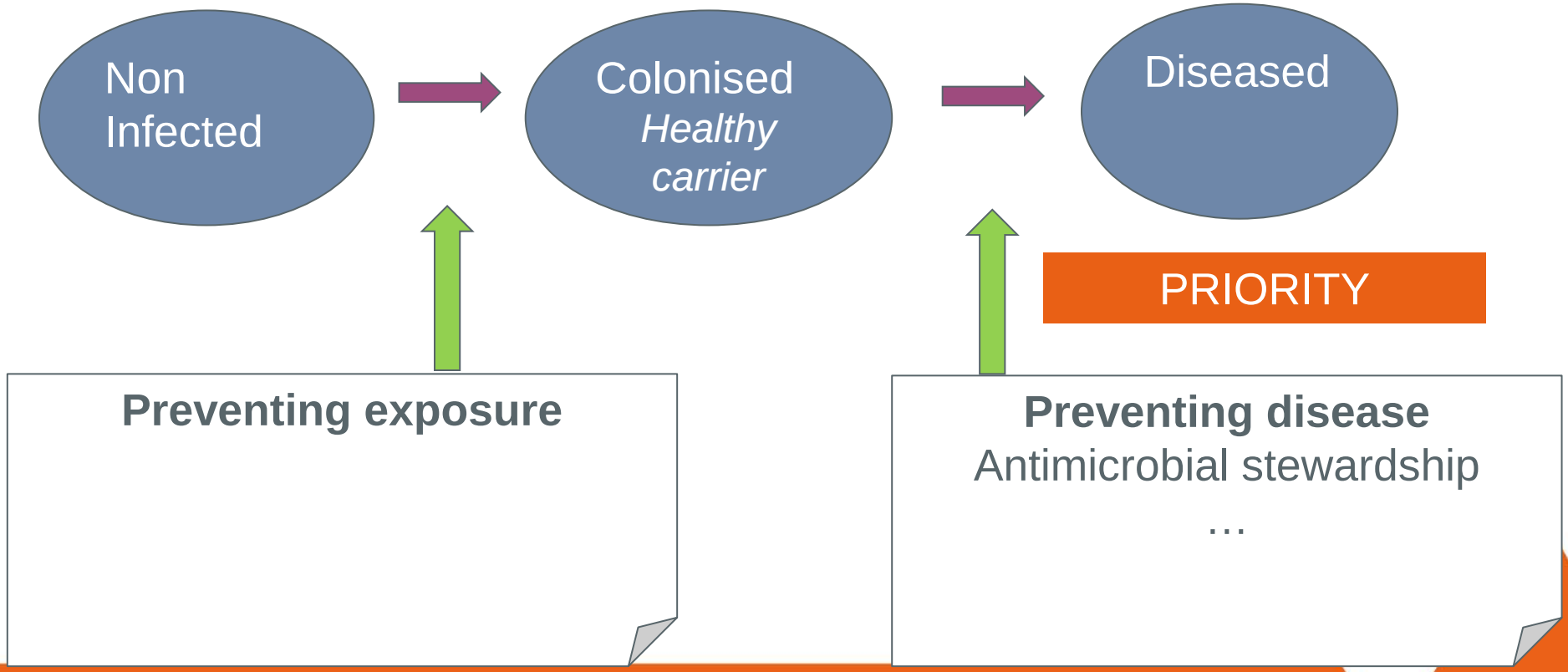
TAKE HOME MESSAGES

Transmission of *CDI* in Belgian hospitals

- Role of the environnement and of healthy *C. difficile* carriers in transmission remains to be elucidated

- Meanwhile…

C. difficile infections: prevention strategies in Belgian hospitals



Transmission of *CDI* in Belgian hospitals

- In Belgium, control of CDI in hospitals should focus on antimicrobial stewardship

Transmission of *CDI* in Belgian hospitals

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Acknowledgements

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Thank you!