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High-value *in vitro* diagnostics in sepsis

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Sepsis: new definition

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Infections associated with dysregulated **host responses** leading to **life-threatening** organ dysfunction

Sepsis V3.0 definition *(JAMA 2016)*

Sepsis: a medical syndrome

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Definition hides well-rehearsed clinical challenges

Need to act quickly with **anti-infection interventions** to limit mortality/morbidity

Non-specific:

-clinical presentations *(limits potential for clinical early warning)*

-host responses *(limits potential for biomarker efficacy)*

Range of potential causative pathogens = *empiric broad-spectrum antimicrobials*

Routine (culture-based) tests = *not time-critical and ?diagnostic accuracy*

Leads to a clinical '*culture*' of educated guess-work

Room for improvement

Room for improvement

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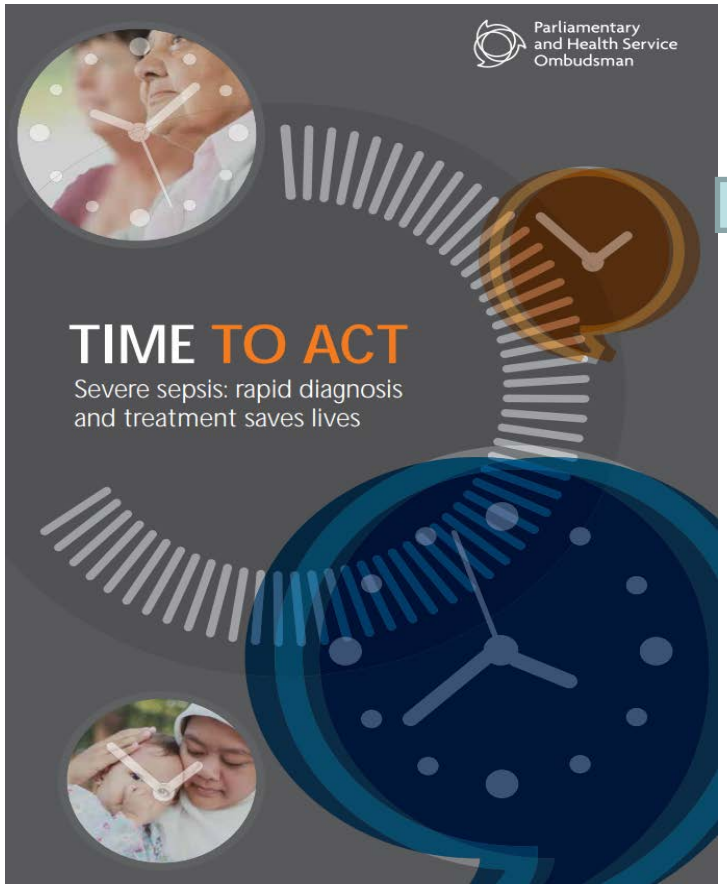

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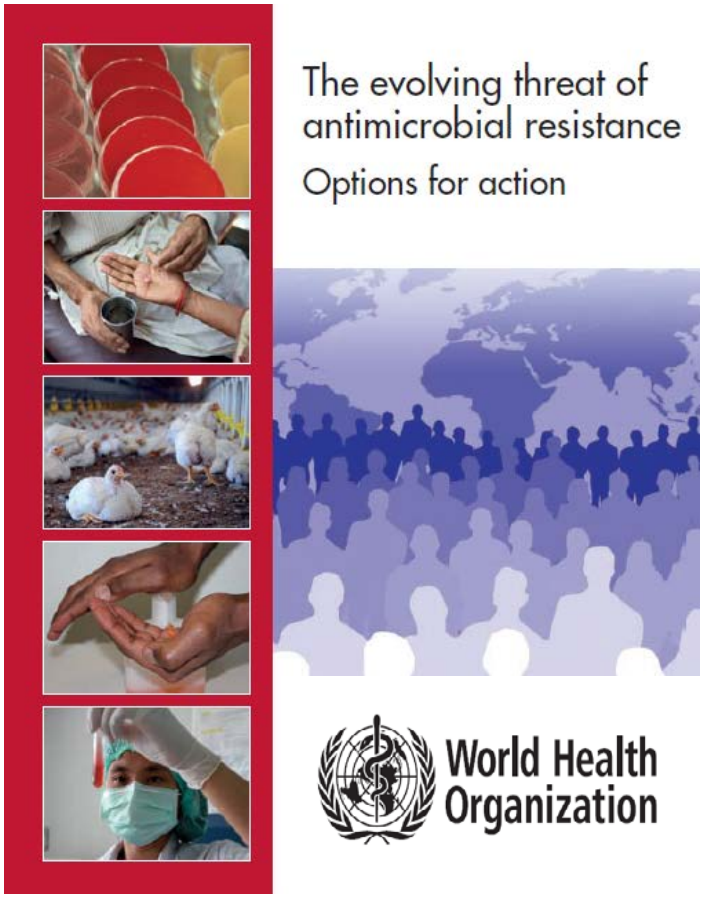
Rapid 'infection' diagnostics (CE-mark):

- Host inflammatory mediators?

- Pathogen detection?

Clinical guidance (first hours) feeding into *'Sepsis CQUINs'*

Unintended consequences



- Surveillance systems
- **Better use of available antibiotics** (humans and animals)
- Hygiene
- Innovation (**rapid diagnostics** and drugs)
- Political commitment to enable

Disruptive diagnostics

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Key diagnostic decision problems to deliver precision

Within hour(s):

Is it infection?

Which, if any, empiric antimicrobial treatments?

Within the day:

What's the causative pathogen and its phenotype?

Can antimicrobial treatments be refined safely?

Within days:

What is optimal duration of antimicrobial treatment?

High-value diagnostics

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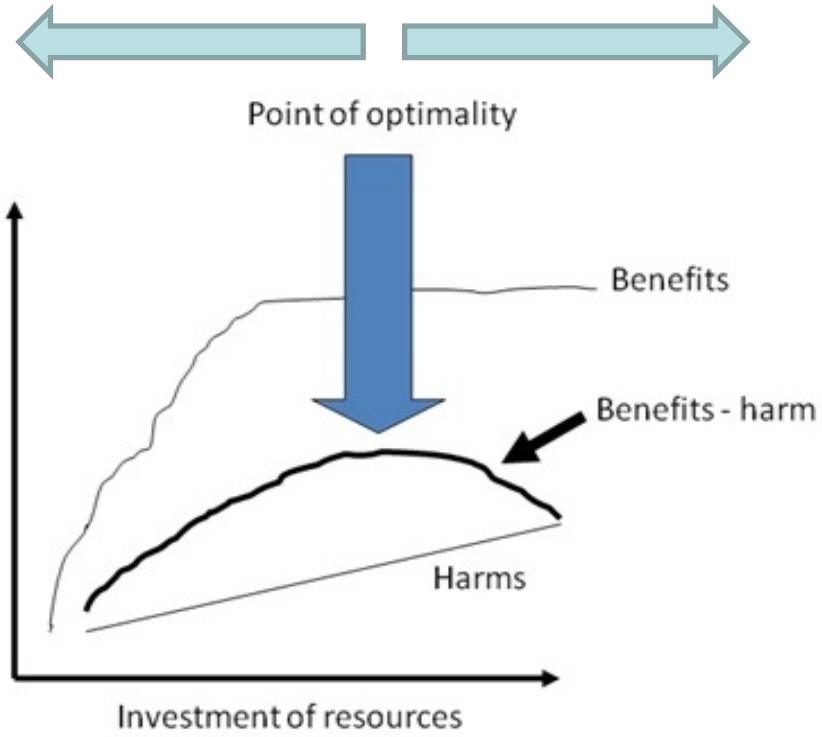
Under diagnosis leading to under treatment **Over diagnosis leading to over treatment**



Adapted from Avedis Donabedian
(and thanks to Muir Gray!)

NIHR research priority

NIHR HTA commissioned research (start 2017)
[responding to recent NICE diagnostic guidances]

Focus on potential over diagnosis/over treatment in sepsis

NHS-wide definitive pragmatic clinical trials:

- HTA 15/116: IVDs to rule-out invasive fungal sepsis (circulating fungal antigens and/or DNA)
- HTA 15/99: IVDs to guide antibiotic duration in sepsis (circulating CRP and PCT)

NIHR research priority

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NHS-wide definitive pragmatic clinical trials aimed at:

-catalysing evidence-base for clinical effectiveness

-biomarkers identified but IVDs not specified

-clinical and cost effectiveness outcomes

-understanding clinical decisions behaviour

-5-year horizon for patient impact

Coordinated/delivered by globally-leading NIHR UK research network

Summary

Rapid infection diagnosis is the key to improvements in sepsis care

Highlighted some key decision problems for care disruption

Donabedian framework to conceptualise high-value IVDs

Important roles for NICE and NIHR to catalyse evidence for IVDs

Max. 5-year horizon to impact, responding to patient need