# Laboratory update - May 2019

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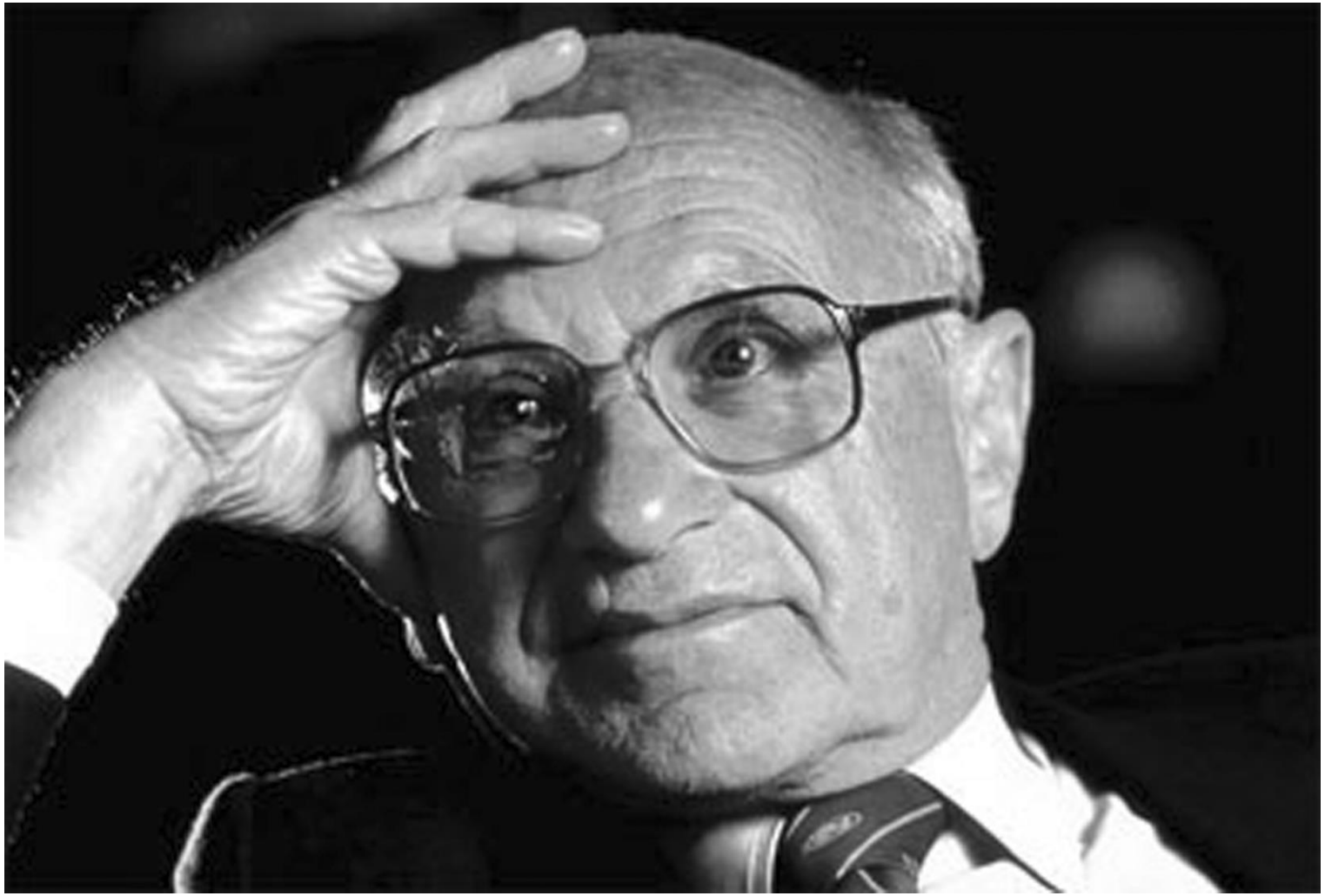
# “Nobody spends someone else’s money as wisely as he spends his own”



# Demand management

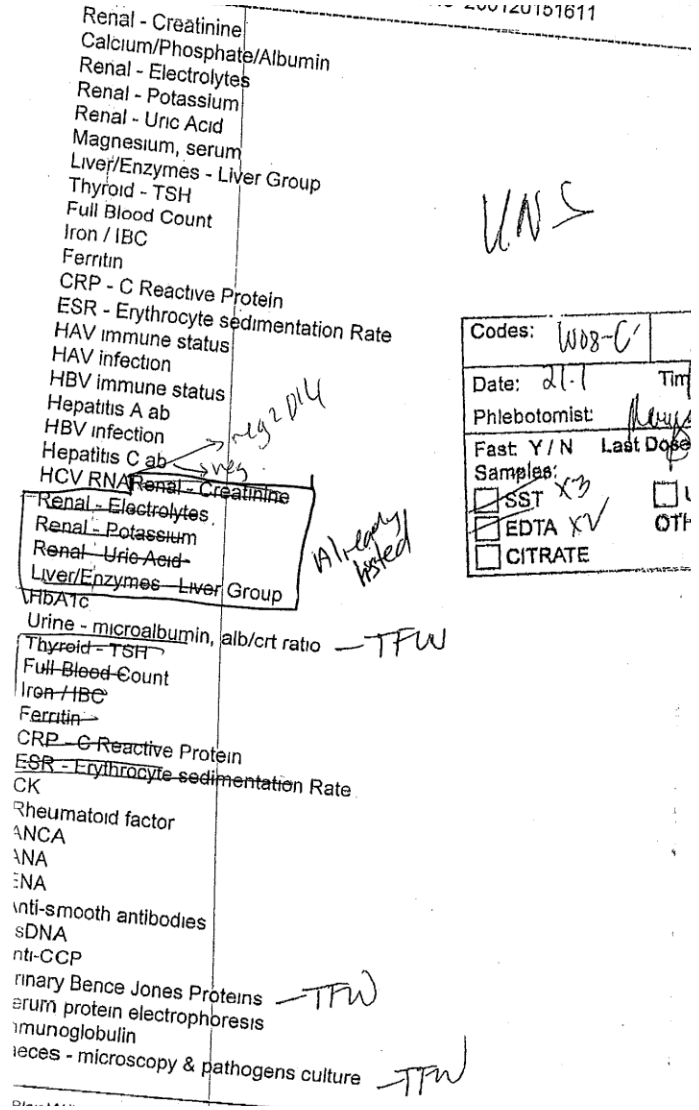
**In all private laboratory contacts**

**To cite:** Fryer AA, Smellie WSA. *J Clin Pathol* 2013, **66**, 62–72.

## Managing demand for laboratory tests: a laboratory toolkit

Anthony A Fryer,[1] W Stuart A Smellie[2]

Emerg …oratory medicine circles, it is often confused with the term 'demand control'. Demand control refers to the use of approaches to *reduce the volume of requests*, while demand management focuses on *ensuring appropriate requesting*. Hence, the latter has an inbuilt quality aspect and may result in increased, as well as decreased, testing (ie, to reduce overordering, underordering, and misordering of tests).[7]

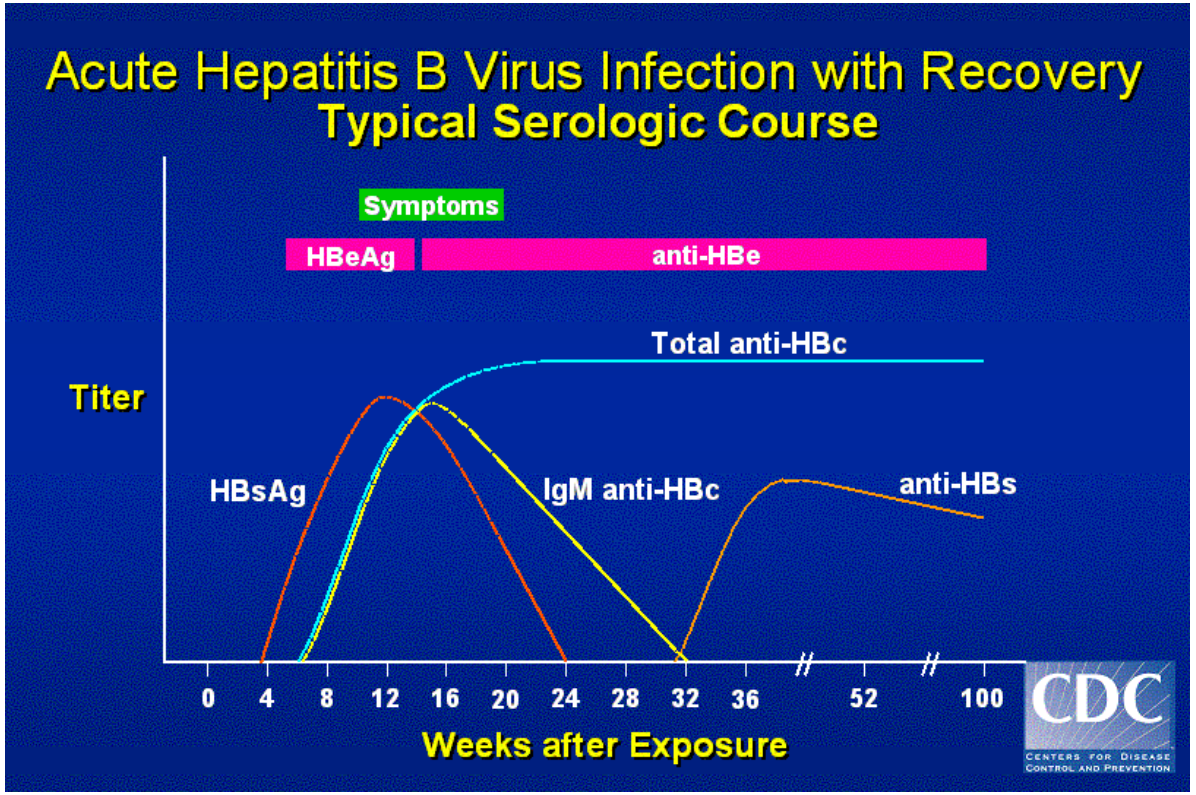


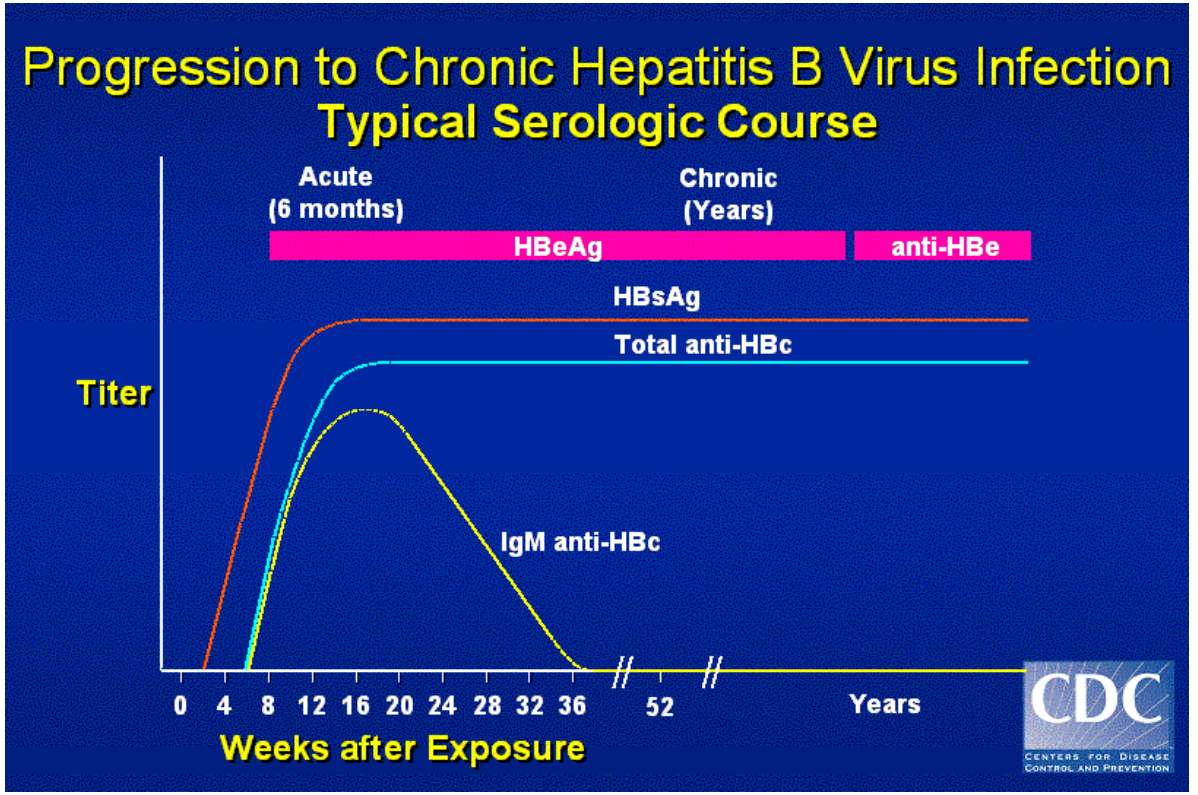
# Demand management in practice

Senior scientist or pathologist review:

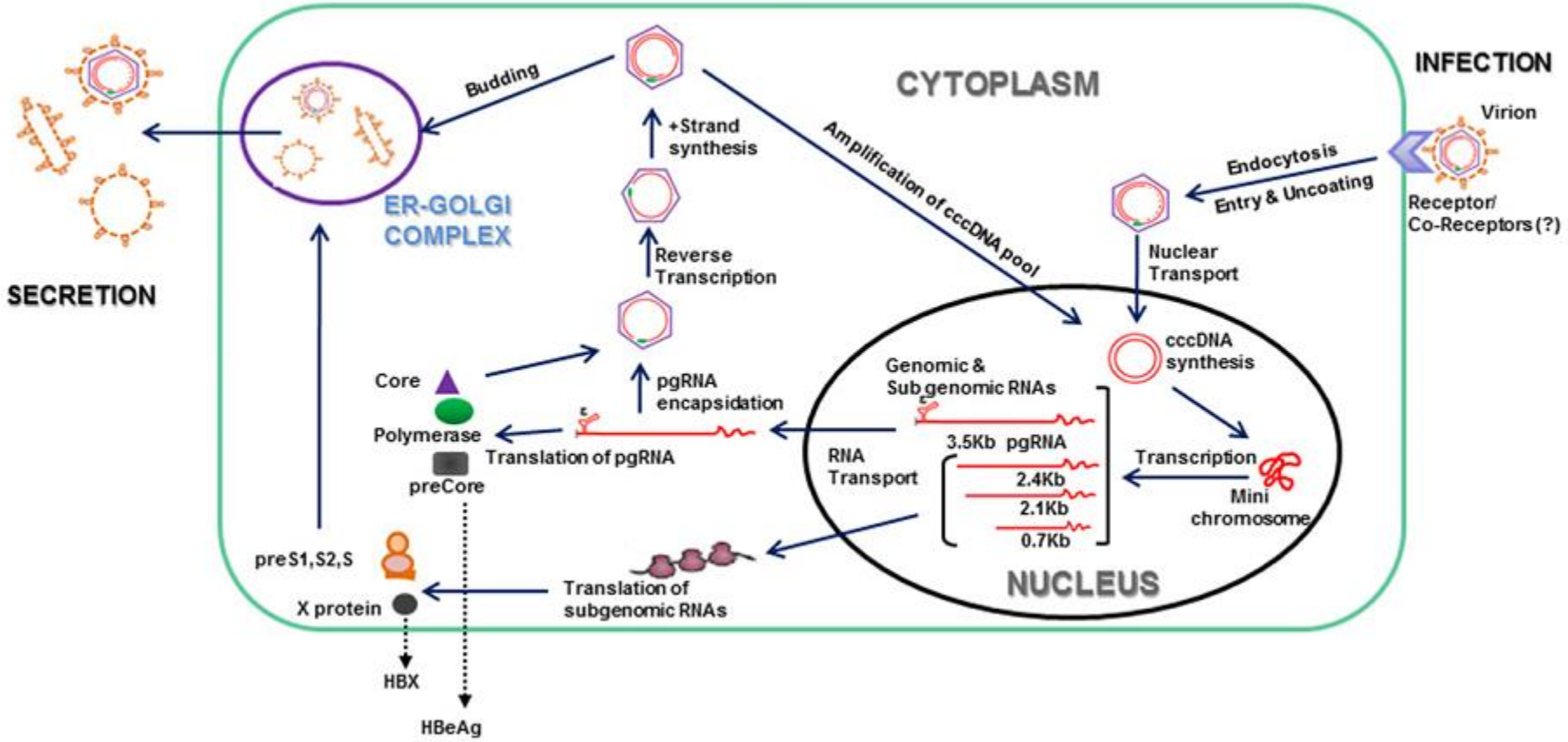
- Expensive requests, e.g. molecular tests
- Frequently mis-requested tests, e.g. TB urine culture, hep A serology
- Improving patient care – HCV validation
- Requirement for relevant clinical details
  - Microbiology
  - Immunology
  - Infectious serology

# Management of hepatitis B



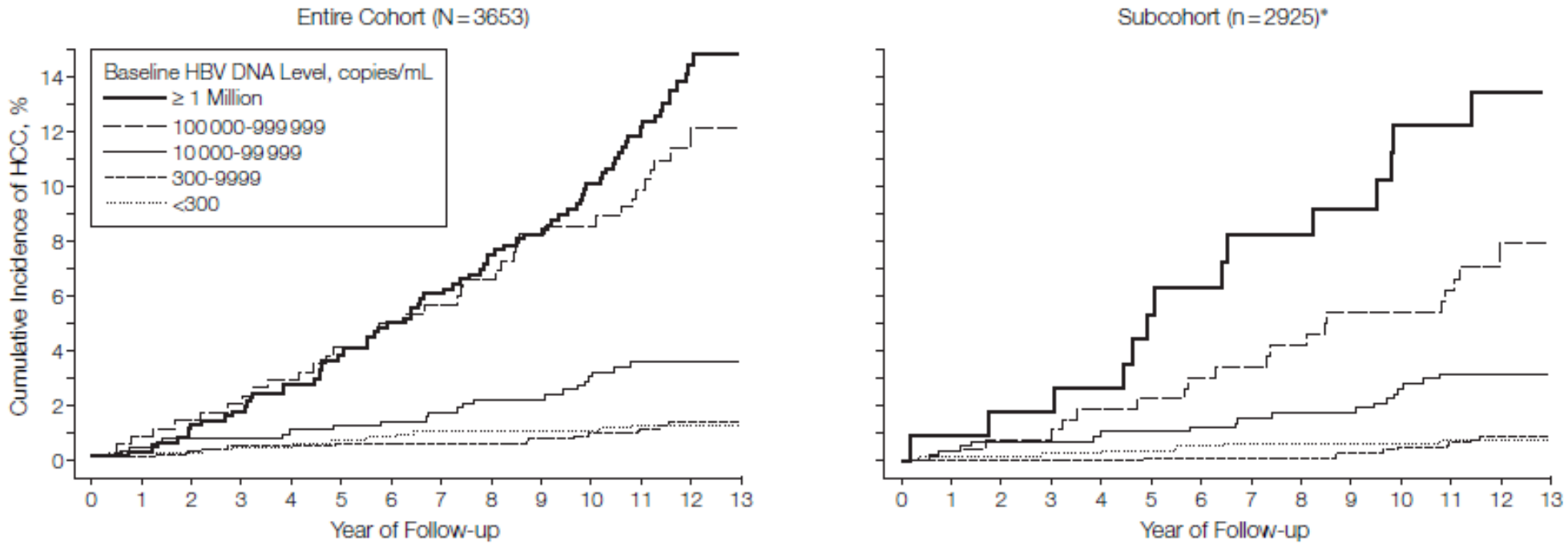
# DNA integration




Journal of Clinical and Experimental Hepatology | December 2012 | Vol. 2 | No. 4 | 353–365

# Natural history chronic HBV

**Figure 2.** Cumulative Incidence of Hepatocellular Carcinoma by Serum HBV DNA Level at Study Entry



# Relevant tests

Hepatitis B serology – what the virus and the body are up to

HBV DNA – viral load

Liver tests – enzymes (ALT) and function (PR, albumin)

Other – markers of cirrhosis (AST, platelets)

# When to test for what

| Clinical scenario | Bloods etc | Notes |
|---|---|---|
| ? Infection – raised ALT | sAg +/- sAb | |
| ? Infection – random check | Take history …… +/- sAg | |
| ? Immune | Take history …. +/- sAb | |
| Needle stick injury – injured | sAg + sAb | |
| Needle stick injury – donor | sAg +/- sAb | |
| Chronic infection monitoring | sAg + sAb +/- eAg, AFP, ALT | eAg only if previously positive |
| Chronic infection monitoring | Anti-Hbe | Only if has been on therapy which have been stopped as eAg negative for > 6 – 12 months |
| Chronic infection on therapy | As above + HBV DNA | If on entecavir or tenofovir and compliant, annually sufficient |
| Chronic infection + cirrhosis | As above + FBC + PR (INR) | |
| Cirrhosis or family history HCC | Six monthly USS | |
| For immunosuppression | sAg, sAb, anti-Hbcore | Need to document on request |

## Testing for HBV infection

There are two main groups of people who should be tested for hepatitis B infection: those who may have been exposed during birth or early childhood and therefore now have chronic hepatitis B infection, and those with a potential exposure as an adult, which may have resulted in acute hepatitis B infection but in most cases will not proceed to chronic infection.

Consider testing people with risk factors for HBV infection, including:[1,13,16]

- Māori, Pacific, South East Asian or Chinese ethnicity*
- Age over 30 years*
- Incomplete or unknown childhood vaccination status*
- Country of birth with high HBV prevalence, e.g. Pacific Islands, China, South East Asia, Middle East and Africa, or travel to those countries
- Mother or close family or household member with HBV infection
- Unprotected sex with an HBV-infected person
- Current or previous injecting drug user

# **Hepatitis B:** treatments now available for primary care

Tenofovir disoproxil and entecavir are once daily oral antiviral medicines, recommended as first-line treatments for patients with chronic hepatitis B; they are now fully subsidised with no restrictions. Clinicians in primary care can help patients benefit from these medicines by testing those with risk factors for hepatitis B and ensuring they receive appropriate treatment in primary or secondary care.

**Arrange follow-up for patients with chronic HBV infection**

Patients with chronic HBV infection should be referred to the Hepatitis Foundation, secondary care*, or treated within primary care.

The Hepatitis Foundation of New Zealand has a national contract to provide clinical support and management in partnership with primary and secondary care, including:[19]

- Initial evaluation after a diagnosis has been made
- Organising ongoing monitoring tests, including blood tests and liver elastography (Fibroscan) assessments
- Patient support, education and access to a community hepatitis nurse

Patients can be referred by:

- Calling the Hepatitis Foundation: **0800 33 20 10**
- Completing and online form: **www.hepatitisfoundation.org.nz/enrol-in-the-hepatitis-b-programme/**

| **Prophylaxis is recommended in patients who are initiated on:** | **Prophylaxis is not necessary in patients who are initiated on:** |
|---|---|
| ■ Cancer chemotherapy<br>■ B-cell depleting agents such as rituximab<br>■ TNF inhibitors such as infliximab, adalimumab, etanercept<br>■ Oral corticosteroids at a dose equivalent to 10 mg of prednisone or greater for 4 weeks or longer | ■ Methotrexate<br>■ Azathioprine<br>■ 6-mercaptopurine<br>■ Intra-articular corticosteroids |

## An overview of HBV management for primary care[11, 13, 23]

| Stage of care | Aspect of care | Tests or criteria |
|---|---|---|
| **Initial assessment (after a diagnosis has been made)** | Assessments of liver health | ■ Complete blood count<br>■ INR<br>■ Liver function tests, including AST, ALT, alkaline phosphatase and total bilirubin<br>■ Liver elastography scan (Fibroscan) – see note below* |
| | Assessments of HBV activity and stage of infection | ■ HBeAg and anti-HBe serology<br>■ HBV DNA levels |
| | Assessments of other blood-borne viruses + hepatitis A (worsens liver complications if concurrent infection) | ■ Hepatitis A, C and HIV serology |
| **Regular lifelong monitoring** | Assessments of HBV activity, stage of infection and liver health | ■ Every six months:<br>– Liver function tests<br>– HBsAg<br>– HBeAg<br>– Alfa-fetoprotein (AFP)<br>– Liver ultrasound or CT scan for patients at high risk of liver cancer†<br>■ Every year:<br>– Complete blood count to assess thrombocytopaenia, as a marker of portal hypertension and cirrhosis |

| | | |
|---|---|---|
| **Treatment** | When to initiate treatment | ■ Treatment is recommended for patients:<br>– With cirrhosis or severe liver disease with any detectable HBV DNA<br>– Who are HBeAg positive and persistently have ALT levels over two times the upper limit of normal **<br>– Who are HBeAg negative patients persistently have ALT levels over two times the upper limit of normal and HBV DNA levels >2000 IU/mL |
| | Prior to initiating treatment, conduct tests which may influence the choice and dose of medicines | ■ Renal function (creatinine clearance) – adjust dose of medicine accordingly, e.g. Table 3<br>■ Pregnancy test for females |
| | Monitoring effectiveness and safety during treatment (in addition to regular monitoring detailed above) | ■ Annual HBV DNA level<br>■ Monitoring of calcium, phosphate and creatinine levels in patients taking tenofovir disoproxil |

* Referral criteria and wait times for liver elastography scans may vary across DHBs. If a liver elastography scan cannot be performed, calculating the ratio of aspartate aminotransferase (AST) levels to platelet concentration (APRI) may be used instead. For further information on calculating an APRI score, see: **https://bpac.org.nz/2016/hepc/default.aspx#assessmen**t

† Patients at high risk are those with severe fibrosis or cirrhosis or a family history of hepatocellular carcinoma

** Persistently elevated ALT levels refers to the results of at least three measurements taken three months apart

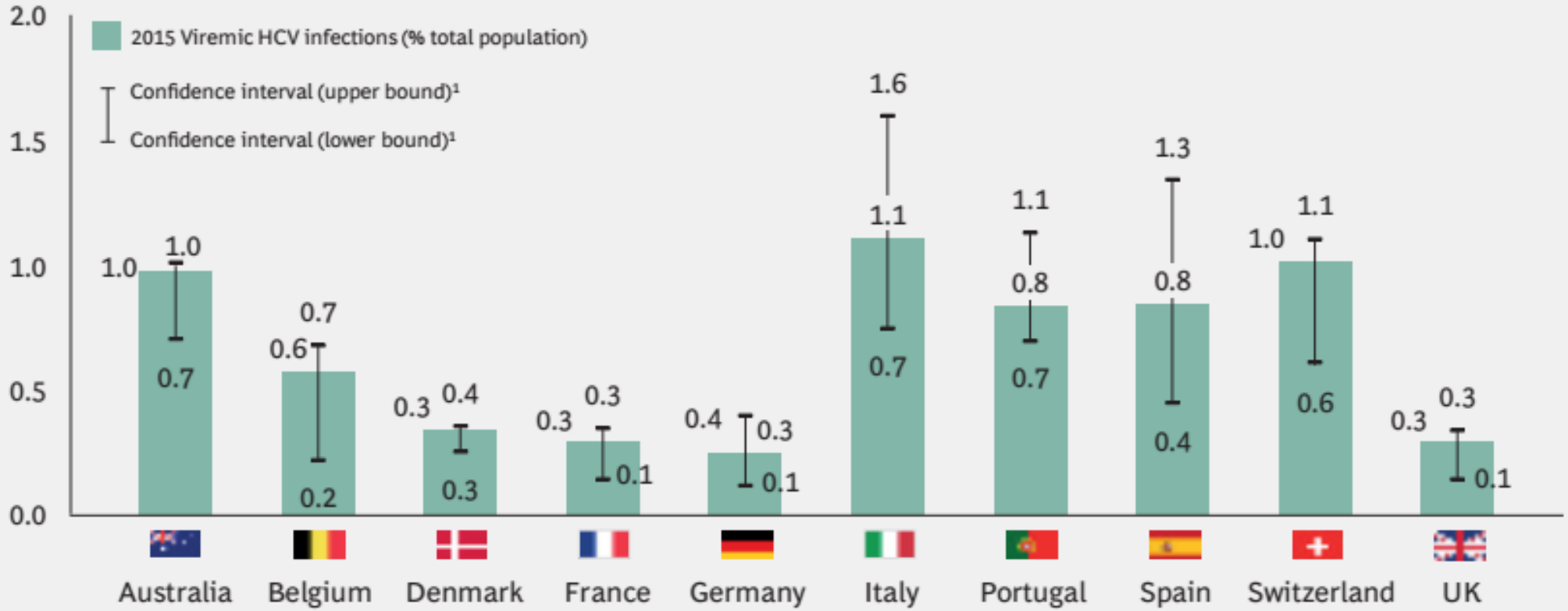
# Update HCV

Elimination goals: 2030

<u>Case finding</u>

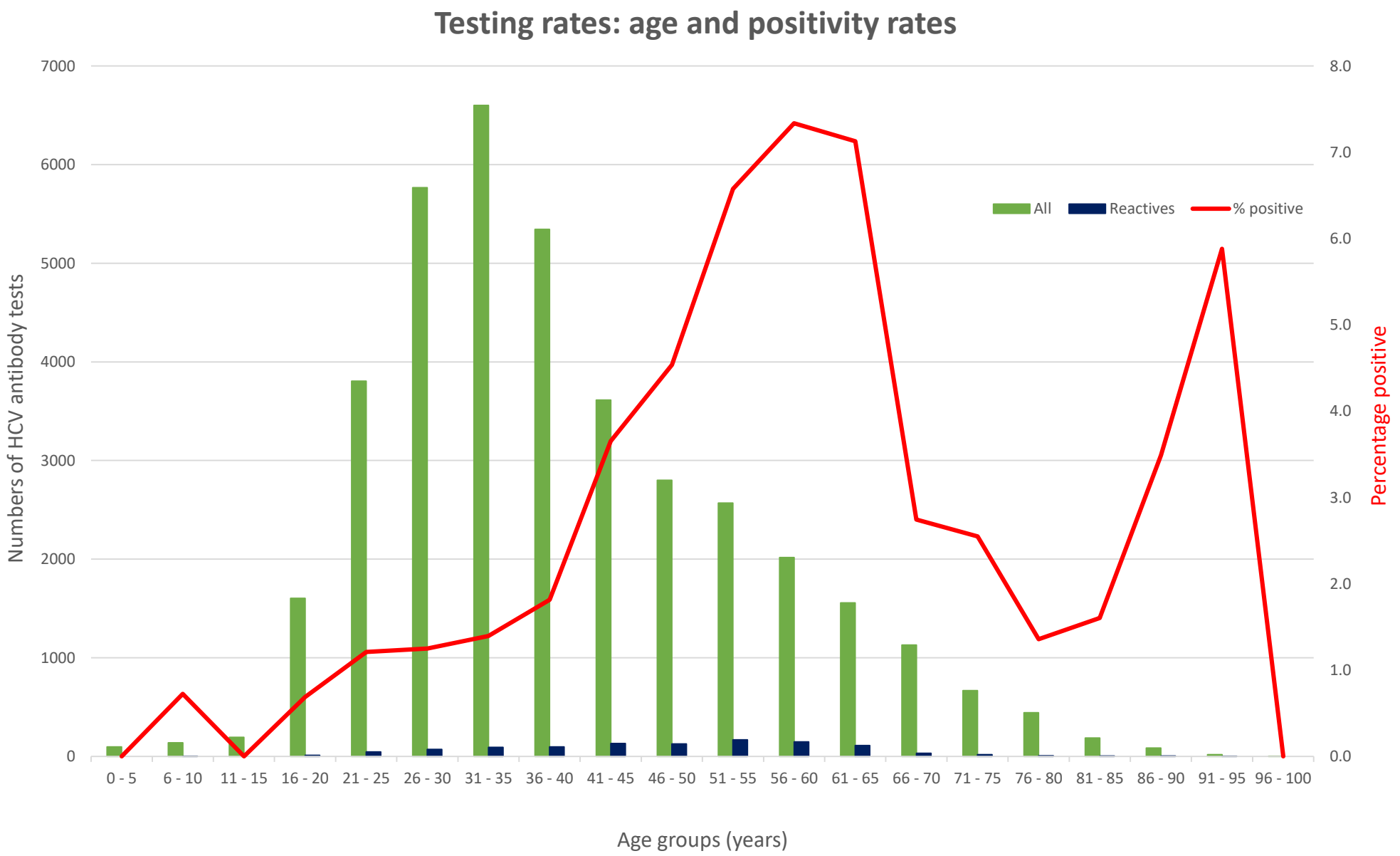
- Targeted screening
- Cirrhosis / HCC presentations
- Testing outside of ‘normal’ healthcare providers
- One-off testing – all adults

## Figure 3 | Estimated HCV prevalence in selected countries (% of total population) in 2015




1. 95% Uncertainty Interval

Source: Razavi and al. (2017); The Polaris Observatory HCV Collaborators (2016)[2]


Testing rates: age and positivity rates
Numbers of HCV antibody tests
Percentage positive
All
Reactives
% positive
7000
6000
5000
4000
3000
2000
1000
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 - 5
6 - 10
11 - 15
16 - 20
21 - 25
26 - 30
31 - 35
36 - 40
41 - 45
46 - 50
51 - 55
56 - 60
61 - 65
66 - 70
71 - 75
76 - 80
81 - 85
86 - 90
91 - 95
96 - 100
Age groups (years)

# **Hepatitis C management** in primary care has changed

A new direct-acting antiviral (DAA) oral regimen for the treatment of hepatitis C, glecaprevir + pibrentasvir (Maviret) will be subsidised without restriction from 1 February, 2019. Treatment with glecaprevir + pibrentasvir is simpler than with Viekira Pak regimens and patients with hepatitis C should now predominantly receive treatment in primary care.

## Treatment with glecaprevir + pibrentasvir is shorter and simpler for clinicians and patients than Viekira Pak regimens

## HCV genotype testing is no longer required

## Treatment with ribavirin is no longer required

### Patients should present prescriptions for glecaprevir + pibrentasvir to an enrolled pharmacy

Prescriptions for glecaprevir + pibrentasvir should be given to the patient to present to a pharmacy, as is typically the case for most medicines subsidised in the community. Similar to the arrangements that have been in place for Viekira Pak regimens, glecaprevir + pibrentasvir will be available at enrolled pharmacies.[4] There is no co-payment required from patients for glecaprevir + pibrentasvir prescriptions. For patients prescribed Viekira Pak regimens or Harvoni, prescriptions need to be sent directly to PHARMAC.

**Pre-treatment assessment to exclude cirrhosis or complicating factors**

- Clinical examination for symptoms and signs
- Laboratory tests for liver disease, hepatitis B, HIV and pregnancy
- Non-invasive liver assessment:
  - APRI calculation
  - Liver elastography (Fibroscan) if available
- Check for medicines interactions:
  - New Zealand Formulary (NZF) interactions checker: **www.nzf.org.nz**
  - OR University of Liverpool HCV medicines interactions checker: **www.hep-druginteractions.org**

If treatment in primary care is appropriate

**Prescribe glecaprevir + pibrentasvir**

- Patients will need to collect their medicine from an enrolled pharmacy
- Alternative arrangements can be made if collection from an enrolled pharmacy is not possible

Treatment lasts eight weeks
Follow-up patients after four weeks of treatment to assess adverse effects

**After treatment has finished**

- Test for cure with an HCV RNA assay or HCV antigen assay conducted 12 weeks after treatment has finished. Order liver function tests at the same time.
- Refer patients to a gastroenterologist if test results are positive 12 weeks after treatment has finished
- Patients with cirrhosis require long-term monitoring for the development of hepatocellular carcinoma
- No further follow-up for HCV complications is required for patients without cirrhosis and with normal liver function tests after treatment
- If patients have ongoing abnormal liver function tests, consider other possible causes
- Annual HCV RNA assays or HCV core antigen assays are recommended for patients with ongoing risk factors, e.g. people who inject drugs. Previous infection does not confer immunity.

# Acute HCV

Used to wait 3 months to see if spontaneously cleared

With Maviret probably treat at diagnosis – public health intervention

# Sputum culture (routine, not TB)

Common specimen, fairly useless

Results probably drive some unnecessary antibiotic prescription

From ‘up-to-date’

> **Bronchitis** — Sputum Gram stain and culture have no role in the evaluation of acute bronchitis in otherwise healthy individuals. Similarly, they are not indicated in the initial evaluation of patients with acute exacerbations of chronic obstructive pulmonary disease.
>
> **CAP** – if good quality sputum can be obtained in patients with pneumonia and:
>
> ICU, failure outpatient therapy, cavitary lesions, active ETOH abuse, severe COPD, pleural effusion
>
> **Hospital acquired pneumonia**

# Sputum culture - audit

*Has it changed management?*

“able to stop antibiotic”

“Pseudomonas isolated – changed antibiotic to cover”

“treated with amox - didn’t put symptoms down to CHF”

“suspected ca - confirmed not infection“

“query pneumonia - didn't continue abs”

# Management of self-limiting respiratory tract infections in adults and children in primary care

November 2015

**1.7** An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- if the patient is systemically very unwell
- if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, intraorbital and intracranial complications)
- if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, and young children who were born prematurely
- if the patient has had ≥ 3 episodes of wet cough lasting >4 weeks during the last 12 months
- if the patient with acute otitis media or acute cough/acute bronchitis is considered unlikely to promptly return for a further consultation in the event of significant clinical deterioration. This includes children aged under 2 years from areas of high socioeconomic deprivation, with household crowding and financial or cultural barriers to health care.
- if the patient is older than 65 years with acute cough and two or more of the following criteria, or older than 80 years with acute cough and one or more of the following criteria:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure
  - current use of oral glucocorticoids.

For these patients, the no antibiotic prescribing strategy and the delayed antibiotic prescribing strategy should not be considered.

# Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study

Myriam Gharbi,[1,2] Joseph H Drysdale,[3] Hannah Lishman,[1,2] Rosalind Goudie,[1,2,4] Mariam Molokhia,[5] Alan P Johnson,[1,6] Alison H Holmes,[1] Paul Aylin[1,2]

*BMJ* 2019;364:l525

## CONCLUSIONS

In elderly patients with a diagnosis of UTI in primary care, no antibiotics and deferred antibiotics were associated with a significant increase in bloodstream infection and all cause mortality compared with immediate antibiotics. In the context of an increase of *Escherichia coli* bloodstream infections in England, early initiation of recommended first line antibiotics for UTI in the older population is advocated.

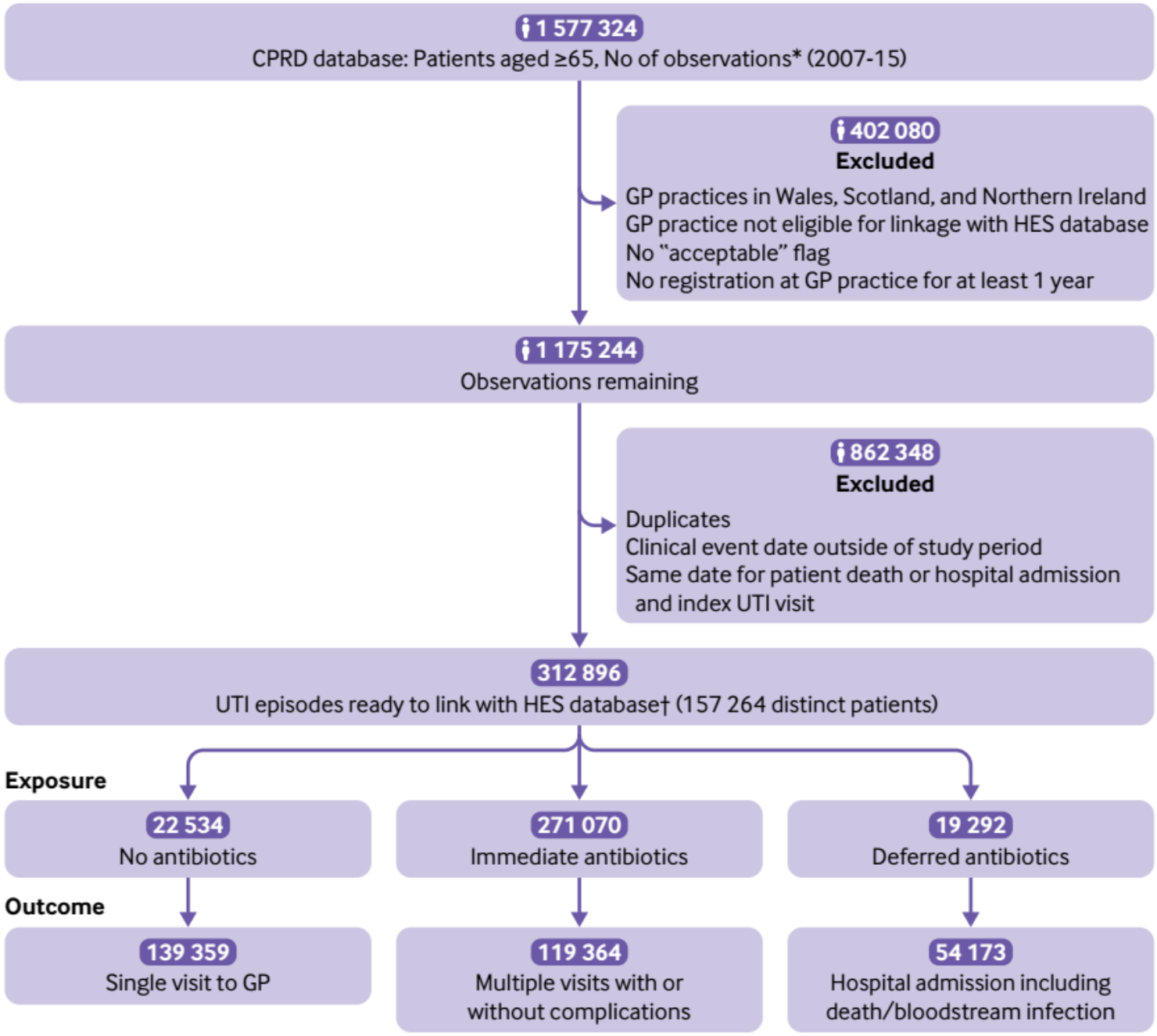

1 577 324
CPRD database: Patients aged ≥65, No of observations* (2007-15)
402 080
Excluded
GP practices in Wales, Scotland, and Northern Ireland
GP practice not eligible for linkage with HES database
No "acceptable" flag
No registration at GP practice for at least 1 year
1 175 244
Observations remaining
862 348
Excluded
Duplicates
Clinical event date outside of study period
Same date for patient death or hospital admission and index UTI visit
312 896
UTI episodes ready to link with HES database† (157 264 distinct patients)
Exposure
22 534
No antibiotics
271 070
Immediate antibiotics
19 292
Deferred antibiotics
Outcome
139 359
Single visit to GP
119 364
Multiple visits with or without complications
54 173
Hospital admission including death/bloodstream infection

**Table 1 | Summary of patients' characteristics and outcomes related to each episode of urinary tract infection (UTI). Values are numbers (percentages) unless stated otherwise**

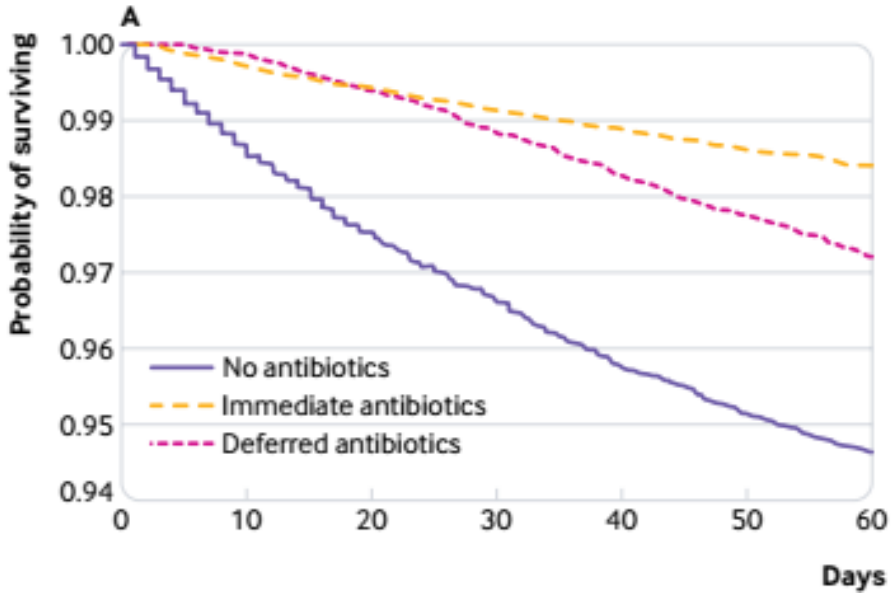
| Characteristics | No with UTI (n=312 896) | Immediate antibiotics (n=271 070) | Deferred antibiotics (n=19 292) | No antibiotics (n=22 534) | P value |
|---|---|---|---|---|---|
| Mean (SD) age (years) | 76.9 (9.2) | 76.3 (9.1) | 79.1 (9.2) | 79.3 (9.5) | |
| Age group (years): | | | | | |
| 65-74 | 136 175 (43.5) | 122 458 (45.2) | 6402 (33.2) | 7315 (32.5) | <0.001 |
| 75-84 | 107 485 (34.3) | 92 856 (34.3) | 6881 (35.7) | 7748 (34.4) | |
| ≥85 | 69 236 (22.1) | 55 756 (20.6) | 6009 (31.1) | 7471 (33.1) | |
| Sex: | | | | | |
| Women | 246 630 (78.8) | 217 843 (80.4) | 13 657 (70.8) | 15 130 (67.1) | <0.001 |
| Men | 66 266 (21.2) | 53 227 (19.6) | 5635 (29.2) | 7404 (32.9) | |
| Mean (SD) Charlson comorbidity index score | 0.36 (0.8) | 0.35 (0.7) | 0.44 (0.9) | 0.44 (0.9) | <0.001 |
| Charlson comorbidity index score ≥1 | 75 563 (24.2) | 63 694 (23.6) | 5492 (28.5) | 6377 (27.9) | <0.001 |
| Immunosuppression | 82 (0.03) | 67 (0.02) | 8 (0.04) | 7 (0.03) | 0.348 |
| Renal disease | 10 215 (3.3) | 8,588 (3.2) | 746 (3.9) | 881 (3.9) | <0.001 |
| Smoking | 12 449 (4.0) | 10 798 (4.0) | 751 (3.9) | 900 (4.0) | 0.818 |
| Recurrent UTI | 68 967 (22.0) | 59 456 (21.9) | 6072 (31.5) | 3439 (15.3) | <0.001 |
| Indwelling urethral catheter | 2627 (0.8) | 1933 (0.7) | 352 (1.8) | 342 (1.5) | <0.001 |
| Hospital admission within 30 days before UTI diagnosis | 35 825 (11.4) | 22 930 (8.5) | 5252 (27.2) | 7643 (33.9) | <0.001 |
| Antibiotics exposure 30 days before UTI diagnosis | 61 832 (19.8) | 49 079 (18.1) | 7173 (37.2) | 5580 (24.8) | <0.001 |
| Symptoms within 30 days before UTI diagnosis† : | 23 502 (7.5) | 19 172 (7.1) | 2021 (10.5) | 2309 (10.2) | |
| Enuresis | 13 (0.01) | 10 (76.9) | 3 (23.1) | 0 | <0.001 |
| Offensive urine | 50 (0.02) | 43 (86) | 5 (10) | 2 (4) | |
| Urgency | 397 (0.1) | 348 (87.7) | 23 (5.8) | 26 (6.5) | |
| Malaise | 688 (0.2) | 527 (76.6) | 69 (10.0) | 92 (13.4) | |
| Fatigue | 694 (0.2) | 607 (87.5) | 39 (5.6) | 48 (6.9) | |
| Confusion | 1459 (0.5) | 895 (61.3) | 241 (16.5) | 323 (22.1) | |
| Haematuria | 2065 (0.7) | 1621 (78.5) | 205 (9.9) | 239 (11.6) | |
| Incontinence | 2159 (0.7) | 1783 (82.6) | 194 (9.0) | 182 (8.4) | |
| Micturition frequency | 3682 (1.2) | 3151 (85.6) | 261 (7.1) | 270 (7.3) | |
| Dysuria | 4158 (1.3) | 3411 (82.0) | 398 (9.6) | 349 (8.4) | |
| Pain* | 9604 (3.1) | 7896 (82.2) | 746 (7.8) | 962 (10.0) | |
| Outcome: | | | | | |
| No (%) with bloodstream infection (95% CI) | 1539 (0.5; 0.5 to 0.5) | 479 (0.2; 0.1 to 0.2) | 413 (2.2; 1.9 to 2.4) | 647 (2.9; 2.7 to 3.1) | <0.001 |
| No (%) admitted to hospital (95% CI) | 51 261 (16.4, 16.2 to 16.5) | 40 022 (14.8, 14.6 to 14.9) | 5165 (26.8, 26.2 to 27.4) | 6074 (27.0, 26.4 to 27.5) | <0.001 |
| Mean (SD) length of stay (days) | 7.1 (15.0) | 6.3 (14.0) | 7.7 (13.2) | 12.1 (20.9) | <0.001 |
| No (%) of deaths at 60 days (95% CI) | 6193 (2.0, 1.9 to 2.0) | 4431 (1.6, 1.6 to 1.7) | 545 (2.8, 2.6 to 3.1) | 1217 (5.4, 5.1 to 5.7) | <0.001 |

**Table 3 | Multivariable logistic regression analysis for bloodstream infection 60 days after diagnosis of urinary tract infection (UTI)**

| Variables | Unadjusted odds ratio (95% CI)* | P value | Adjusted† odds ratio (95% CI)* | P value |
|---|---|---|---|---|
| Antibiotic exposure: | | | | |
| Antibiotic at first visit | Reference | | Reference | |
| Deferred antibiotic | 12.36 (10.81 to14.13) | <0.001 | 7.12 (6.22 to 8.14) | <0.001 |
| No antibiotic | 16.70 (14.81 to 18.83) | <0.001 | 8.08 (7.12 to 9.16) | <0.001 |
| Age group (years): | | | | |
| 65-74 | Reference | | Reference | |
| 75-84 | 2.37 (2.08 to 2.71) | <0.001 | 1.59 (1.39 to 1.82) | <0.001 |
| ≥85 | 3.13 (2.73 to 3.58) | <0.001 | 1.67 (1.44 to 1.93) | <0.001 |
| Sex: | | | | |
| Men | Reference | | Reference | |
| Women | 0.25 (0.23 to 0.28) | <0.001 | 0.45 (0.40 to 0.50) | <0.001 |
| Region: | | | | |
| North of England and Yorkshire | Reference | | | |
| Midlands and East of England | 1.02 (0.89 to 1.18) | 0.74 | | |
| South of England | 0.86 (0.75 to 0.99) | 0.03 | | |
| London | 0.90 (0.74 to 1.09) | 0.28 | | |
| Index of multiple deprivation (fifths): | | | | |
| 1st (least deprived) | Reference | | Reference | |
| 2 | 1.00 (0.86 to 1.16) | 0.98 | 0.97 (0.83 to 1.14) | 0.74 |
| 3 | 1.07 (0.92 to 1.25) | 0.38 | 1.04 (0.89 to 1.22) | 0.58 |
| 4 | 1.35 (1.15 to 1.58) | <0.001 | 1.21 (1.03 to 1.42) | 0.02 |
| 5th (most deprived) | 1.39 (1.18 to 1.65) | <0.001 | 1.18 (0.99 to 1.40) | 0.06 |
| Charlson comorbidity index score (0-12) | 1.35 (1.29 to 1.40) | <0.001 | 1.10 (1.04 to 1.16) | <0.001 |
| Immunosuppressed | 5.06 (1.26 to 20.31) | 0.02 | | |
| Renal disease | 1.61 (1.28 to 2.02) | <0.001 | | |
| Smoking | 1.20 (0.95 to 1.52) | 0.16 | | |
| Year of UTI: | | | | |
| 2007-08 | Reference | | Reference | |
| 2008-09 | 0.70 (0.45 to 1.10) | 0.12 | 0.67 (0.42 to 1.07) | 0.09 |
| 2009-10 | 0.74 (0.48 to 1.16) | 0.20 | 0.66 (0.42 to 1.05) | 0.08 |
| 2010-11 | 0.97 (0.63 to 1.51) | 0.90 | 0.86 (0.55 to 1.36) | 0.53 |
| 2011-12 | 0.90 (0.58 to 1.40) | 0.65 | 0.77 (0.49 to 1.22) | 0.26 |
| 2012-13 | 1.98 (1.30 to 3.01) | 0.001 | 1.57 (1.01 to 2.42) | 0.04 |
| 2013-14 | 3.38 (2.24 to 5.12) | <0.001 | 2.72 (1.77 to 4.19) | <0.001 |
| 2014-15 | 4.52 (2.98 to 6.83) | <0.001 | 3.46 (2.25 to 5.32) | <0.001 |
| Symptoms <30 days before UTI diagnosis | 1.20 (1.01 to 1.44) | 0.04 | | |
| Antibiotic prescribed <30 days before UTI diagnosis | 1.26 (1.12 to 1.42) | <0.001 | | |
| Admitted to hospital 30 days before diagnosis | 10.45 (9.44 to 11.57) | <0.001 | 3.94 (3.54 to 4.39) | <0.001 |
| Indwelling urethral catheter | 3.60 (2.66 to 4.89) | <0.001 | | |
| Recurrent UTIs | 0.77 (0.67 to 0 0.88) | <0.001 | 0.86 (0.75 to 0.99) | 0.04 |
| Interaction antibiotic exposure and recurrence | 1.27 (1.15 to 1.41) | <0.001 | | |

**Table 2 | Distribution of antibiotics prescriptions among participants prescribed immediate treatment during their index visit for a urinary tract infection (UTI)**

| Antibiotics | No (%) (n=271 070) |
|---|---|
| Trimethoprim | 148 333 (54.7) |
| Nitrofurantoin | 51 745 (19.1) |
| Cephalosporins | 31 090 (11.5) |
| Amoxicillin/clavulanic acid | 25 616 (9.4) |
| Quinolones | 11 995 (4.4) |
| Pivmecillinam | 1084 (0.4) |
| Macrolides | 747 (0.3) |
| Penicillinase resistant penicillins | 323 (0.1) |
| Benzylpenicillin and phenoxymethylpenic | 70 (0.03) |
| Aminoglycosides | 27 (0.01) |
| Clindamycin | 3 (<0.01) |
| Carbapenems | 3 (<0.01) |
| Polymyxin | 1 (<0.01) |



The main limitations of our study are common to observational studies using routinely collected electronic health record data, and include unmeasured and residual confounders, missing data and potential biases, such as confounding by indication, misclassification biases, or inconsistencies in coding within and between practices and over time.

Patients were identified and included in our study based on a clinical diagnosis recorded using a coding system. Therefore, most of the cases were suspected UTIs, with only a minority based on a laboratory confirmed diagnosis. Separate microbiology data with UTI confirmation and drug sensitivities were unavailable. We used a pragmatic approach to

We cannot exclude an alternative non-urinary source for the bloodstream infections. The origin of the bloodstream infections is not often specified in hospital episode statistics or CPRD. In the context of

## Conclusion

Results from this large population based cohort study suggest a significant increase in the risk of bloodstream infection and all cause mortality and the rate of hospital admission associated with no antibiotics and deferred antibiotics compared with immediate antibiotics in older adults with a diagnosis of UTI in primary care. Our study suggests the early initiation of antibiotics for UTI in older high risk adult populations (especially men aged >85 years) should be recommended to prevent serious complications.

| Gram negative bacteria 2018 Dunedin community (% sensitive) | Number tested | Amoxycillin | Amoxycillin/ Clavulanate | Amoxycillin/ Clavulanate (cystitis only) | Cefalexin (cystitis) | Tetracycline/ doxycycline | Nitrofurantoin (cystitis) | Ciprofloxacin* | Trimethoprim (cystitis) | Cotrimoxazole* | Fosfomycin (cystitis) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *E. coli* (all) | 7267 | 58% | 78% | 91% | 95% | | 99% | | 75% | | |
| *E. coli* (urine) | 7170 | 58% | 78% | 91% | 95% | | 99% | | 75% | | |
| *E. coli ESBL urines** | 194 | R | | 73% | R | | 97% | 35% | 27% | 29% | 98% |
| *Proteus mirabilis* | 266 | 92% | 99% | 99% | 92% | | R | 98% | 79% | | |
| *Salmonella* spp | 106 | 91% | | | | | | 87% | | 98% | |
| *Pseudomonas aeruginosa* | 410 | | | | | | | 88% | | | |
| *Haemophilus influenzae* | 420 | 68% | 81% | | | 99% | | 99% | | 73% | |