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Validation and application of POCT in the framework of respiratory tract infections

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27/02/2024, Amersfoort, The Netherlands

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Agenda

- POCTs in general and in infectious diseases
  - Definition POCT
  - Relevance and market
- POCTs for diagnosis of respiratory infections
  - Types of POCT
  - POCT SARS-CoV-2 and influenza as an example
  - Challenges POCT
  - Future trends

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POCTs in general and in infectious diseases

New Africa/Adobe Stock

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Definition POCT

- Form of testing in which the analysis is performed where healthcare is provided close to or near the patient: "point of impact" testing
- Various definitions: near patient testing (NPT), bed side testing, physicians office testing (POL), off site testing, alternative site testing, etc.
- In practice, POCT may be undertaken in many locations:
  - home use, self testing, pharmacy, paramedical support, ambulance, nursing home or aged care centre, primary care, rural (remote) hospital or health clinic, emergency admissions, operating theater, delivery room, critical care facility in hospital, hospital ward, …
- Although in most countries highly trained laboratory professionals are required to follow extensive government regulations to ensure quality test results, specific testing requirements are not identified for POCT (may be performed by individuals without formal laboratory training). results of POCT in hospitals remain under responsibility of central lab!

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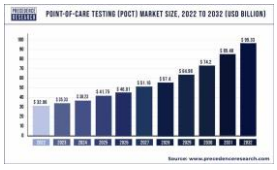
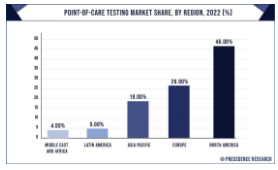
POCT: relevance and market





Point-of-Care Testing (POCT) Market Size, Report 2023 To 2032 (precedenceresearch.com)

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Applications POCT in infectious diseases

- Provide information to directly influence the timely and proper care of patients
- Enable the effective surveillance, prevention and control of infectious disease outbreaks
- Eliminates need for ordering additional, unnecessary tests
- Detect and prevent the spread of infectious diseases by ensuring that patients are diagnosed at an earlier stage, decreasing transmission to others
- Address issues around antimicrobial stewardship by avoiding the inappropriate use of antimicrobials for presumed infectious diseases
- POCT can also be used to distinguish infectious diseases such as influenza virus from other illnesses

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- To assess the availability, use and impact of point-of-care testing devices (POCT) in the EU/EEA Member States and the UK for communicable diseases under EU surveillance
- Data collection: 2014 - 2019
- Broad literature search: 350/11.728 publications fully extracted

Assessment-of-point-of-care-testing-devices-for-infectious-disease-surveillance.pdf (europa.eu)

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POCT device turnaround time

Time to result	Number of POCT devices
Less than 10 min	33
10 min or more but less than 30 min	145
Half an hour or more but less than 1 hour	53
1 hour – 1.5 hours	63
Not recorded	379

Tests able to provide results in <10 minutes may be most preferable for use in primary care.
If a patient is admitted to the hospital, longer turnaround times may be tolerable.

Assessment-of-point-of-care-testing-devices-for-infectious-disease-surveillance.pdf (europa.eu)

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Comparison of intended and actual use of the POC devices

Intended use		Actual use				
		Antibiotic resistance	Diagnosis/detection	Diagnosis/detection and antibiotic resistance	Diagnosis/detection and other	Other
	Antibiotic resistance	1	0	0	0	0
	Diagnosis/detection	0	168	0	2	7
	Diagnosis/detection and antibiotic resistance	1	2	1	0	0
	Diagnosis/detection and other	0	1	0	4	0
	Other	0	1	0	0	12

Assessment-of-point-of-care-testing-devices-for-infectious-disease-surveillance.pdf (europa.eu)

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POCT sensitivity and specifity

Sensitivity	Nr of POCTs	Specificity	Nr of POCTs
99% and above	63	99% and above	126
95%-98%	53	95%-98%	103
90%-94%	45	90%-94%	44
85%-89%	47	85%-89%	21
80%-84%	30	80%-84%	9
75%-79%	27	75%-79%	3
70%-74%	25	70%-74%	8
65%-69%	11	65%-69%	1
60%-64%	25	60%-64%	6
59% or less	57	59% or less	6
Not recorded	392	Not recorded	522

Assessment-of-point-of-care-testing-devices-for-infectious-disease-surveillance.pdf (europa.eu)

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POCTs for diagnosis of respiratory infections

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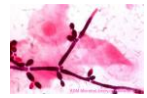
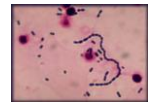
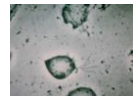
Gram stain



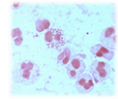
Candida albicans



Group A streptococcal pharyngitis



trichomonas



Gonorrhoeae

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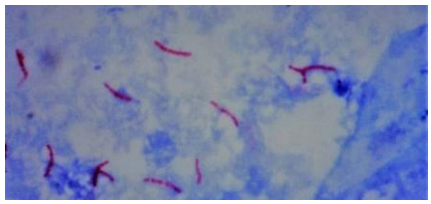

Mycobacterium tuberculosis
- Acid fast

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Differentiation bacterial vs viral infection: CRP

- Compared with usual care, CRP-POCT to guide antibiotic prescribing for (lower and upper) RTIs in primary care can reduce antibiotic prescribing at index consultations
- No significant difference between CRP-POCT and usual care in the number of patients with clinical recovery at 7 and 28 days (7 days, 51.7% vs. 52.8%: RR 1.03, 95%CI 0.93 to 1.14, p = 0.53; 28 days, 77.8% vs. 75.3%: RR 0.95, 95%CI 0.70 to 1.28, p = 0.72)
- Significant increase in re-consultations among patients in the CRP-POCT group (13.5% vs. 9.7%: RR 1.33, 95%CI 1.14 to 1.57, p = 0.0004)
- No significant effect of CRP-POCT in the rates of clinical recovery, resolution of symptoms, hospital admissions, referrals to secondary care, or in the ordering of further investigations.

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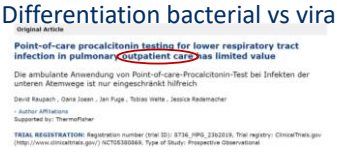
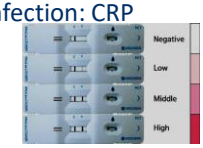
Differentiation bacterial vs viral infection: CRP





- 110 patients presenting with LRTI at their GP
- 3 patients (2.7%) had PCT values above the threshold of 0.25 µg/L without proven bacterial infection
- 7 patients with typical radiological signs of pneumonia without elevated POCT PCT levels
- Limited sensitivity and specificity in distinguishing pneumonia from bronchitis or exacerbations of chronic respiratory disease

⟹ PCT is a marker of severe bacterial infections and not suitable for milder infections in outpatient care.

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Antigen detection: Urinary Ag-test

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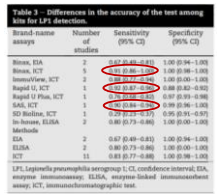
L. pneumophila uAg-test

- Legionellosis caused >80% of infections by *L. pneumophila* serogroup 1
- Community-acquired and nosocomial pneumonia, associated with poor prognosis
- 21 included studies, 5772 patients, 1368 suspected legionellosis
- Pooled sensitivity: 0,79 (0,71-0,85)
- Pooled specificity: 1,00 (0,99-1,00)



- uAg-tests can be useful for early detection due to it's moderate sensitivity but high specificity: positive results could aid in early appropriate treatment
- No recent reports on worldwide distribution of *Legionella* species and serogroups since 2002: epidemiological data should be updated to decide on the usefulness of uAg-tests

Respiratory Investigation. 2022. 60:205-214

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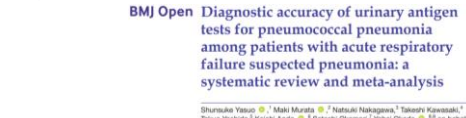
S. pneumoniae uAg-test



- *S. pneumoniae* most common cause of community acquired pneumonia in adults
- Main cause of pneumonia causing acute respiratory failure
- 90-day mortality 25-30% (very high)
- 30 studies
- 12 366 patients, 1548 (12,5%) with pneumococcal pneumonia
  - Positive sputum gram stain
  - Positive blood culture
  - Positive culture respiratory specimen (sputum, pleural fluid, BAL, ...
- Pooled sensitivity: 0.66 (0.62-0.69) (moderate)
- Pooled specificity:0.90 (0.85-0.93) (high)
  - No pediatric patients
  - No immunocompromised patients
  - Unable to check effect of prior antibiotic use
  - All studies used BinaxNow-Sp
  - uAg-test does not give info on AMR
  - If patient had recently a pneumococcal pneumonia, false positive results for several weeks after onset

⟹ uAg-test can be used to rule in rather than to rule out pneumococcal pneumonia

BMJ Open 2022;12:e057216. doi:10.1136/bmjopen-2021-057216

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Antigen detection: Agglutination test

Clinical performance of rapid antigen tests in comparison to RT-PCR for SARS-COV-2 diagnosis in Omicron variant: A systematic review and meta-analysis

Zahra Eslami Mohammadie[1] | Saeed Akhlaghi[2] | Saeed Samaeinasab[3] | Shakiba Shaterzadeh-Bojd[4] | Tannaz Jamialahmadi[5] | Amirhossein Sahebkar[5,6,7,8]

- 18 studies included
  - Pooled sensitivity: 0,671 (0,595-0,721)
  - Pooled specificity: 1,000 (0,997-1,000)
  - FDA-approved kits showed a better performance than WHO-approved kits with a sensitivity of 0.728 (0.620–0.815)
  - Nasal swabs showed a higher sensitivity compared with nasopharyngeal swabs
  - Sensitivity for samples with a CT-value >25 was 0.108 (0.048–0.227)

⟹ Rapid antigen tests show impaired performance for COVID-19 diagnosis when the Omicron variant is circulating, particularly in samples with low viral loads.

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Pathogen detection: Nucleic acid based POCTs

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SARS-CoV-2 as an example

- Evaluation of the performance of molecular and antigen-based POCTs in confirmed, suspected, or probable COVID19 cases compared with that of laboratory-based RT-PCR in real-life settings.
- 123 eligible publications:
  - 97 assessing antigen POCTs
  - 26 studies assessing molecular POCTs
- Best performing molecular POCTs
  - Simplexa® COVID-19 Direct kit, Cepheid Xpert® Xpress SARS-CoV-2, cobas ® SARS-CoV-2, AQ-TOP™, BioFire® Respiratory Panel 2.1, and SAMBAII Coronavirus SARS-CoV-2 Testsystem.
- Best performing antigen-based POCTs
  - COVID-VIROALLIN® and GenBody COVID-19 Ag test (2 evaluations each) .

Fragkou et al. Clinical Microbiology and Infection 29(2023) 291e301

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SARS-CoV-2 as an example: Nucleic acid based POCTs

POCT device name	Pathogen covered	Description	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Time to results
ID NOW (Alere i)	SARS-CoV-2	Isothermal amplification	0.86 (0.78-0.92)	0.99 (0.98-0.99)	<15 min
Cobas ® SARS-CoV-2, AQ-TOP	SARS-CoV-2	Isothermal amplification	0.98 (0.93-1.00)	0.96 (0.91-0.99)	20 min
Samba II	SARS-CoV-2	Real-time PCR	0.98 (0.93-1.00)	0.98 (0.94-0.99)	95 min
Filmarray Respiratory 2.1 panel	18 viruses and 4 bacteria	MX Real-time PCR, Tm	0.98 (0.89-1.00)	1.00 (0.93-1.00)	45 min
Simplexa	SARS-CoV-2	Real-time PCR	1.00 (0.89-1.00)	1.00 (0.98-1.00)	90 min
Xpert Xpress	SARS-CoV-2	MX Real-time PCR	0.98 (0.95-0.99)	0.96 (0.93-0.97)	36 min

Fragkou et al. Clinical Microbiology and Infection 29(2023) 291e301

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SARS-CoV-2 as an example

- Factors influencing the sensitivity of the assays:
  - Type of RDT:
    - Molecular POCTs yielded significantly higher sensitivity rates than antigen-based POCTs.
  - Conformity to IFU:
    - Antigen-based POCTs that were performed following IFU had a higher but not statistically significant sensitivity than that yielded with non eIFU conforming testing: 73.1%(95%CI,68.7e77.1%) versus 67.7% (95%CI,61.9-73.0%)
  - Target population:
    - Antigen-based POCTs used as screening tools in the general population, sensitivity decreased to 49.3% (95%CI, 39.7-59.1%).
    - Sensitivity decreased to 46.2% (95%CI,36-56.6%) when the test was performed >7 days since symptom onset.
- Specificity rates were high across all subgroup analyses.

Fragkou et al. Clinical Microbiology and Infection 29(2023) 291e301

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Influenza as an example

- Rapid on-site molecular Point of Care Testing during influenza outbreaks in aged care facilities
  - 6,500 residents aged ≥65 years who reside in 63 ACFs
  - Descriptive epidemiological study into 82 respiratory clusters reported across 63 ACFs on the use of on-site molecular PCR POCT (Xpert® Xpress Flu/RSV) as an early intervention.
  - POCT results were confirmed by laboratory-based PCR assay
  - 80 clusters of ILI reported
    - 73 confirmed viral outbreaks across 43 ACFs (20 ACFs had multiple outbreaks) comprising of 1,084 ILI cases (861 residents and 223 staff)
    - 43/73 influenza outbreaks
    - 27 clusters of ILI (34%) POCT was performed
    - 53 clusters (66%) were tested using routine laboratory-based PCR laboratory only

Escarate et al. Aust NZ J Public Health. 2022; 46:884-8

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Influenza as an example

- 12 influenza and 1 RSV outbreak confirmed by POCT
- Outcomes:
  - Sensitivity and specificity Xpert® Xpress Flu/RSV for influenza A: 100%
  - Antiviral prescription:

Antiviral prescription during outbreak	POCT (n=12)		Non-POCT (n=31)	
	Within 24hrs	Within 72hrs	Within 24 hrs laboratory confirmation	Within 72 hrs laboratory confirmation
As prophylaxis	9 (75%)	10 (83%)	10 (32%)	15 (48%)
As treatment	10 (83%)	11 (92%)	18 (58%)	24 (77%)

Escarate et al. Aust NZ J Public Health. 2022; 46:884-8

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Influenza as an example

- Comparison of ACF influenza outbreaks by POCT and laboratory PCR

Table 3a: Comparison of ACF Influenza outbreaks by POC and laboratory PCR testing.

	POCT (n=12)	Non-POCT (n=31)	p-value
Median Length of Outbreak (days)	18.5 (IQR 14.0 – 24.3)	15.0 (12.5– 20.0)	0.2685
Median days until PHU notification	2.0 (IQR 1.0 – 4.0)	5.0 (3.0-8.0)	0.0038*
Median resident clinical attack rate (%)	12.0% (IQR 9.0% – 19.0%)	11.0% (4.0%-19.0%)	0.3712
Median staff clinical attack rate (%)	4.0% (1.0% – 8.0%)	2.0% (1.0%-4.0%)	0.6679
Number of ACFs administering prophylaxis – during outbreak	11.0 (92.0%)	22.0 (71.0%)	0.15
Number of ACFs administering treatment – during outbreak	11.0 (92.0%)	29.0 (94%)	0.83
Number of ILI hospitalisations	24 (n=181) (13.3%)	76(n=357) (21.3%)	0.02*
Number of Influenza-related deaths	7(n=181) (3.9%)	26(n=357) (7.3%)	0.12

Note:
*Indicates statistical significance (p<0.05).

Escarate et al. Aust NZ J Public Health. 2022; 46:884-8

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Current challenges POCT

- Low diagnostic accuracy (e.g. sensitivity and specificity), particularly at low concentrations of infectious agent in clinical specimens
- Connectivity of POCT technology to integrate POCT results with hospital- and lab-based information
- Cost of a test
- Complexity of sampling eg nasopharyngeal swab vs saliva

➡ POCT should be: Affordable; Sensitive; Specific; User-friendly; Rapid and robust; Equipment-free; and Deliverable to end-use (WHO ASSURED criteria)

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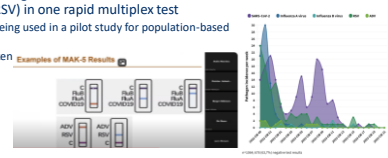
Future trends POCT

- Improved technologies: accuracy, speed, easier interpretation
- Reduction of workload
- Cover more therapy and disease areas
- Syndromic and multiplex testing
- Introducing AI to improve communication across health care systems
- Use of easier to collect samples eg breath, saliva, capillary blood
- Holistic health monitoring: a diagnostic kit to detect infectious diseases at home (e.g., COVID-19, flu strains, RSV) in one rapid multiplex test
  - eg MAK-5 test which is now being used in a pilot study for population-based testing
  - Selftest, picture should be taken and uploaded for validation

MAK 5 – VACCELERATE



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