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Prevention and control of outbreaks of seasonal influenza in long-term care facilities:

a review of the evidence and best-practice guidance

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Contents

Foreword

Dr Zsuzsanna Jakab, WHO Regional Director for Europe

The population in the WHO European Region is ageing rapidly with the proportion of people aged 65 and older forecast to increase from 14% in 2010 to 25% in 2050. The WHO Regional Office for Europe, through the European health policy framework Health 2020, aims to significantly improve the health and well-being of populations, reduce health inequalities, strengthen public health and ensure people-centric health systems that are universal, equitable, sustainable and of high quality. These aims are in line with the new Sustainable Development Goals (Goal 3: Ensure healthy lives and promote well-being for all at all ages) and are based on a life-course approach to increase the effectiveness of interventions throughout a person's life.

In the case of the elderly, the chances of spending their later years in good health and well-being vary within and between countries. As the elderly, as well as other vulnerable groups, are most likely to be severely affected by seasonal influenza, WHO recommends they be vaccinated, and vaccination is a key intervention in the WHO Regional Office for Europe's "Strategy and action plan for healthy ageing in Europe, 2012–2020".

However, uptake of seasonal influenza vaccine in these groups is low in many countries and is decreasing overall in the European Region, while influenza outbreaks in long-term care facilities for the elderly and disabled are not uncommon. The WHO Regional Office for Europe provides support to Member States for the prevention and control of influenza through a wide range of activities, but guidance specifically focused on the prevention and control of healthcare-associated influenza infections was lacking. This best practice document incorporates current evidence and tools to prevent and manage outbreaks of influenza in long-term care facilities. It has been developed with the WHO Collaborating Centre for Pandemic and Epidemic Research at the University of Nottingham, United Kingdom, and with input from influenza experts from the European Region network.

We hope it will be a useful tool to reduce the burden of severe influenza among vulnerable groups in the Region.

Authors

This document was developed by Louise Lansbury (Research Fellow) and Professor Jonathan Nguyen-Van-Tam, WHO Collaborating Centre for Pandemic and Epidemic Research at the Health Protection and Influenza Research Group, Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, United Kingdom. The work was coordinated by Dr Caroline Brown, Programme Manager of the Influenza & Other Respiratory Pathogens Programme, WHO Regional Office for Europe.

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Pasi Penttinen

WHO headquarters:

Nahoko Shindo

WHO Regional Office for Europe:

Diane Gross
Dina Pfeifer
Ana Paula Coutinho Rehse

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Abbreviations and acronyms

AGP	aerosol generating procedure
ARI	acute respiratory infection
BiPAP	bi–level positive airway pressure ventilation
ECDC	European Centre for Disease Prevention and Control
CDC	Centers for Disease Control and Prevention, Atlanta, USA
CI	confidence interval
EU	European Union
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCW	health care worker
ILI	influenza-like illness
IPC	infection prevention and control
IPD	invasive pneumococcal disease
ITT	intention-to-treat
ITTI	influenza-confirmed intention-to-treat
IR	incidence rate
LTCF	long-term care facility
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NAI	neuraminidase inhibitor
NNTB	number needed to treat benefit
NNTH	number needed to harm
NPI	non-pharmaceutical interventions
OCT	outbreak control team
OR	odds ratio
PCV	pneumococcal capsulate vaccine
POC	point of care
PPE	personal protective equipment
PPV	pneumococcal polysaccharide vaccine
ppm	parts per million
RCT	randomized controlled trial
RR	risk ratio
RSV	respiratory syncytial virus
SARI	severe acute respiratory infection
SARS	severe acute respiratory syndrome
SARS–CoV	severe acute respiratory syndrome coronavirus
SR	systematic review
WHO	World Health Organization

Definition of terms

Acute respiratory infection – An acute respiratory tract disease caused by an infectious agent, usually commonly circulating viruses including influenza viruses, parainfluenza viruses, rhinoviruses, RSV, human metapneumovirus, human coronaviruses 229E, NL63, OC43, and HKU1, adenoviruses and certain enteroviruses. Although symptoms may vary, it is typically rapid in onset and may include fever, cough, coryza, sore throat, shortness of breath, and wheezing.

Aerosol-generating procedures with increased risk of pathogen transmission – Medical procedures reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission via the generation of infectious particles typically under 5µm diameter, known as 'aerosols' or 'droplet nuclei', which have the potential to reach the lower respiratory tract when inhaled.

Airborne transmission – Spread of an infectious agent through aerosols or droplet nuclei that can remain infectious whilst suspended in the air over long distances and time.

Clinical attack rate – The proportion of a susceptible population who develop symptomatic illness after a specified exposure to an infectious agent.

Cohorting – Placement of patients with the same laboratory-confirmed pathogen (or unconfirmed but with similar clinical features and an epidemiological link) in the same designated unit, ward or area (with or without the same staff).

Contact transmission – Spread of an infectious agent through physical contact with people or objects (*direct contact transmission* through physical contact between an infected host and a susceptible host; *indirect contact transmission* through contact of a susceptible host with a contaminated object, also known as *fomite spread*).

Disinfection – A process to eliminate all viable pathogenic microorganism except bacterial spores from inanimate objects.

Droplet transmission – Spread of an infectious agent through droplets (typically >10µm diameter) which are usually generated by an infected person during coughing, sneezing and talking and which are deposited on the conjunctivae, mouth, nasal, throat or pharyngeal mucosa of another person. Droplets may be inspired but are too large to reach the lungs and travel only short distances (<1m) from the source; unlike droplet nuclei or aerosols, droplets behave ballistically and drop out of the air quickly after release.

GRADE (Grading of Recommendations Assessment, Development and Evaluation) – A systematic and explicit approach to grading the quality of evidence and the strength of recommendations. Evidence is rated as high, moderate, low or very low quality based on study design (RCTs start as high quality, observational studies as low quality) which is then upgraded or downgrading according to evaluation of methodological flaws within component studies, consistency of results across studies, generalizability of the research results across the wider patient base, and the magnitude of the effect (1).

Hand hygiene – A general term referring to any action of hand cleansing with the aim of reducing transient microbial flora.

Infection prevention and control – Infection prevention and control (IPC) is the practical discipline concerned with i) preventing health care-associated infection in patients, health care workers, visitors and other persons associated with health care facilities; and ii) preparing health care facilities for promptly detecting and responding to communicable diseases crises.

Intention–to–treat (ITT) analysis – Analysis of people taking part in a trial based on the group to which they were originally allocated, regardless of whether they dropped out of the trial, failed to comply with the treatment, or switched to another treatment. ITT analyses are frequently used to inform health care decision-making as they reflect what actually happens in real-life situations.

Isolation precautions – Measures designed to minimize the risk of transmission of infections. They are often referred to as IPC precautions. Isolation precautions are typically separated into: standard precautions (these should always be in place for all patient care) and additional precautions (these are required in particular circumstances and comprise Contact, Droplet and Airborne Precautions).

Long–term care facility (LTCF) – A facility that provides care to people who are unable to live independently in the community.

Medical gloves – Disposable gloves used during medical procedures, including examination gloves (sterile or non–sterile), surgical gloves, and medical gloves for handling chemotherapy agents.

Medical mask – Also known as a surgical or procedure mask. As personal protective equipment, a facial mask is intended to protect caregivers and health-care workers against droplet-transmitted pathogens, or to serve as part of facial protection for patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions or excretions. In this document, the term refers to disposable medical masks only.

Non-pharmaceutical interventions – Actions, other than vaccination and the use of medications, that can be taken by individuals, households and communities to prevent or limit the spread of infectious diseases. These may include isolation, quarantine, social distancing, restrictions on movement and travel, external decontamination, hygiene, and precautionary protective behaviour.

Particulate respirator – A type of facial mask sealed to the face which has an integral filtering device or in which the entire facepiece is a filtering medium.

Personal Protective Equipment – Specialized clothing or equipment worn for protection against infectious materials.

Respiratory hygiene – The practice of correctly covering the nose and mouth when coughing or sneezing (using tissues, a medical mask, sleeve or flexed elbow) followed by hand hygiene in order to reduce the dispersal of respiratory secretions that may contain infectious particles.

Visibly soiled hands – Hands on which dirt or body fluids are readily visible.

Summary

Seasonal influenza is an acute viral infection that spreads easily from person to person, causing annual epidemics which peak during the winter in temperate regions of the world. Influenza can affect anyone but some people, including the very young, the elderly, pregnant women and those with underlying diseases, obesity or a weakened immune system are at higher risk of developing severe infection, requiring hospitalization, and possibly leading to death.

Health care-associated influenza infections and influenza outbreaks in long–term care facilities (LTCFs) are well–documented. These outbreaks have the potential to spread rapidly among residents, staff and visitors and to cause severe illness and death among residents.

Description of the guidance:

This document is specifically focussed on the prevention and control of health care-associated influenza infection and influenza outbreaks in such LTCFs, where residents are frequently elderly, frail and debilitated and influenza virus may be introduced through newly admitted residents, visitors or staff. However, the general principles contained in this guidance will also be transferable, to allow for prevention and better control of outbreaks of acute respiratory illness caused by other respiratory pathogens in LTCFs, as well as being applicable to similar facilities such as boarding schools, homes for looked-after children, military barracks and places of detention. The primary target audience of the guidance is health care professionals involved in the provision of care within LTCFs (i.e. professional staff working in homes), not only as a point of reference during an outbreak situation but also as a framework to help them develop their own policies relevant to an individual institution. Preventing and controlling influenza outbreaks in LTCFs requires a multi–faceted approach including vaccination, training and information provision, ongoing surveillance and early detection, transmission-based infection prevention and control precautions, and the use of antivirals where appropriate. Having a committed and strong planning and management team in LTCFs is a key element in successfully implementing prevention and control measures. It also helps to ensure that each staff member feels valued and understands the important responsibility that they play on an individual basis to prevent and control the spread of infection at all times, not only during an outbreak situation.

The main document comprises:

- an introduction to the concepts discussed in the guidance;
- specific guidance on influenza outbreak prevention and control in LTCFs, which is considered in the following domains:
    - pre–outbreak measures: routine measures to prevent infection,
    - early recognition of a possible outbreak,
    - control measures to be taken during an influenza outbreak, including the use of antivirals as treatment and post–exposure prophylaxis,
    - actions to be taken at the end of the outbreak;
- a summary table outlines the principles of the recommendations according to the above domains;
- Annex A contains links to checklists and work-aids for use by LTCFs;
- Annex B provides a review of the population at risk and burden of disease in that population, an overview of the epidemiology of influenza and modes of transmission of the virus, and an evaluation of the evidence for the key recommendations;
- Annex C contains supporting tables summarizing the available evidence reviewed.

Cross–reference is made to other WHO guidelines for supplemental information on hand hygiene and infection prevention, and control of epidemic and pandemic–prone acute respiratory infections in health care settings.

Introduction and scope of the guidance

This evidence review and best practice guidance is the second phase of a collaborative project carried out by the Influenza and Other Respiratory Pathogens Programme at the WHO Regional Office for Europe and the WHO Collaborating Centre for Pandemic and Epidemic Research at the Health Protection and Influenza Research Group at the University of Nottingham School of Medicine, and is in response to requests from WHO European Member States for guidance in the management of outbreaks of seasonal influenza in long-term care facilities.

Current practice to prevent and control outbreaks of influenza in LTCFs in European Member States was described in the first phase of the project and has been used to inform the development of this

guidance[1]. This has been supplemented by a review of the current evidence available for the different interventions to prevent and control outbreaks of influenza in LTCFs, using published systematic reviews whenever possible to help describe good practice.

In the context of this document, the term 'long-term care facilities' (LTCFs) is used to encompass residential care homes and nursing homes that provide care to people who are unable to live independently in the community due to advanced age or physical or mental disability. Residents of such facilities are frequently elderly, often have multiple co-morbidities, including dementia, and may have complex nursing requirements. However, in some Member States, LTCFs may also provide care to younger adults who have skilled nursing requirements. Although the focus of the guidance is LTCFs providing care for a predominantly elderly population, all guiding principles outlined in this guidance are also applicable to other closed or semi-closed adult communities where outbreaks of influenza may be problematic, including those facilities where the residents may be younger but still have nursing needs, and rehabilitation and palliative care facilities. Facilities in which the residents are children (e.g. orphanages and boarding school), and other facilities with closed populations of generally healthy people, including prisons and military training camps, will not be specifically covered in this guidance, although the same guiding principles are valid and should be considered for implementation in other types of settings.

Depending upon the type of facility and the nursing needs of the residents, services are provided by a range of staff including care assistants with few formal health care qualifications, registered nurses, domestic staff, catering and administrative staff, and with additional ambulatory health services provided by external providers such as general practitioners (GPs) and other health care professionals not directly affiliated to the facility. In several care models in Europe individual residents in LTCFs will retain their pre-admission GP (following the principle of 'cradle to grave' continuity of care). This means that a LTCF will often not have its own single medical care provider; instead the residents in the LTCF will have different GPs. This can be a problem for outbreak recognition, because a GP attending resident A (only) may not be involved in the care of residents B,

[1] Guidance was reviewed from the following countries: Estonia, France, Germany, Greece, Ireland, Republic of Moldova, Netherlands, Slovenia, Spain, Sweden, the United Kingdom (separate guidelines from each of England, Northern Ireland, Scotland, and Wales), and Uzbekistan

C and D. Thus, an outbreak may not be recognized as quickly or reliably as it would be in the case of a single medical care provider.

The WHO European Region includes 53 Member States covering a vast geographic area, with considerable demographic variation and differences in political and health and social care infrastructure. This best practice document provides generic guidance to help public health authorities and institutions to prevent and control influenza outbreaks and therefore needs to be tailored according to specific national and local circumstances.

GUIDANCE

Routine and pre-outbreak measures

Planning and administration

Written policies

- The conditions and levels of complexity in LTCFs vary within and between countries. Policy-makers and health administrators should identify strategies with optimal cost–effectiveness ratios based on the facilities' potential for sustainable and continuous quality improvement.
- The management of every LTCF should ensure that written policies are in place which cover:
  - immunization policy for residents and staff, that includes influenza;
  - establishment of an infection prevention and control (IPC) infrastructure for the LTCF, to support IPC activities. An IPC program should include some form of surveillance for infections, an epidemic control program, education of employees in infection control methods, policy and procedure formation and review, an employee health program, a resident health program, and monitoring of resident care practices. The program also may be involved in quality improvement, patient safety, environmental review, antibiotic monitoring, product review and evaluation, litigation prevention, resident safety, preparedness planning, and reporting of diseases to public health authorities;
  - a written outbreak management plan which includes outbreak recognition (definitions, thresholds for suspicion of an outbreak), communication channels (including an upward notification 'tree' or pathway for all facility staff), operational measures, staff contingency plans, and visitor restriction policies, and consideration of antiviral treatment and prophylaxis strategy;
  - policy for staff that experience influenza-like illness (ILI) symptoms to stay home until symptoms have resolved;
  - description of the Outbreak Control Team terms of reference and staffing;
  - a visitor policy for the peak influenza season, which deals specifically with visitors who have symptoms of ARI.

The management of all LTCFs should appoint a named staff member to take responsibility for the development, implementation and regular review of influenza prevention and control policies and protocols.

Training and education

The management of all LTCFs should ensure that all new staff receives induction training to include vaccination policy, infection control methods, policy and procedures, and information about influenza (including its impact, recognition of suspected cases, communication channels, measures to be instigated in a potential outbreak situation, and staff exclusion policies).

- Staff education is an ongoing process and regular re-training on infection control methods, policies and procedures should be given to all staff members. Centralized staff training records should be held by the facility to identify staff members requiring training updates.
- The management of LTCFs should continually strive to improve staff compliance with infection control measures, for example through quality management (including links with patient safety), risk management (such as rapid reporting of adverse events or errors), audits of professional practices and evaluating performance.
- The roles of staff and their authority should be clearly defined in order to empower them to follow the outbreak control plan.

Provision of supplies

It is the responsibility of the management of LTCFs to ensure that there are always adequate provisions of supplies, human resources and the facilities necessary to encourage high compliance with standard and transmission-based IPC precautions. There must always be adequate supplies of the following (for routine use and sufficient to cover 'outbreak surge demand'):

- hand hygiene facilities (soap, clean running water, disinfectant hand rub, disposable paper towels);
- personal protective equipment (PPE) for resident care (medical masks, gowns, gloves, waterproof aprons, respirators (for those facilities with residents requiring tracheal or other complex airway care));
- appropriate materials for cleaning and disinfection.

Rationale:

LTCFs have a broad staff base and may include people with little or no formal health care training. Managers of these facilities therefore have an important role to ensure that all staff has ongoing

training on the importance and practice of infection control, and that the facilities are available for IPC measures to be implemented to a satisfactory standard.

During the SARS outbreak, compliance with IPC measures was found to be associated with HCWs' perception that their facilities had clear policies and protocols, that the management had a positive attitude towards occupational health and safety and provided training in IPC practices (2). The management of LTCFs therefore have a pivotal role in creating a strong institutional climate in which staff feels valued, with continuous accessibility to the training resources, clear infection control policies and supplies and facilities required to promote compliance with infection control practices.

Vaccination of staff

- Annual influenza vaccination should be offered to all staff who will potentially have contact with LTCF residents, unless contraindicated.
- The management of LTCFs should be responsible for maximizing the uptake of influenza vaccine by staff prior to the onset of the flu season.
- A specific staff member should be identified to take responsibility for coordination of the staff vaccination programme in the facility.
- The immunization status of all staff should be recorded annually, or at the commencement of employment for new staff members, who should be offered seasonal influenza vaccine if they have not received it for the current season.
- Vaccine administration should be documented in their staff record and also communicated to their GP if administered through another source.
- Information of the vaccination status of staff should be readily available to the Public Health authorities in case of an outbreak and to generate vaccine coverage rates.
- Management of the LTCF should provide feedback on vaccination coverage to staff members (for example, by displaying vaccine coverage charts on noticeboards, giving badges to vaccinated staff).

Vaccination of residents

- All residents should be offered repeat annual influenza vaccination prior to the onset of the influenza season, unless contraindicated.

- New residents who have not been vaccinated against seasonal influenza for the current season, should be offered a catch-up vaccination if they have missed the round of vaccination offered to other residents.
- Residents (or their next-of-kin if the resident is incapable of providing informed consent) should be provided with adequate information about the vaccine to enable them to make an informed decision about whether to be vaccinated or not. It is recognized that in some circumstances, residents may not be mentally or legally capable of giving informed consent and may also be without an identifiable guardian or next-of-kin. The establishment of legal guardianship of such residents for the purposes of allowing medical procedures including vaccination would need to be resolved by in-country legislation.
- Regular visitors of residents should also be advised about influenza vaccination in order to protect themselves and to protect those they are visiting.
- Vaccine administration should be documented in the residents' health care records.
- Vaccination with polysaccharide 23-valent pneumococcal vaccine (*once only basis) should also be offered to residents and receipt documented in their care records. New residents without prior evidence of receipt of pneumococcal vaccination should also be offered this vaccine. *Annual re-vaccination is not required for this vaccine.

Rationale:

There is evidence that vaccinating the elderly in LTCFs may provide some protection against influenza-like illness, pneumonia, hospitalization and mortality (Annex C1). However, the effectiveness of vaccination against these outcomes is generally small and the quality of the evidence low and based on observational studies. Most countries recommend vaccinating this group due to the high risk of influenza-related complications. Based on the current evidence base it is reasonable to continue to support this preventative policy as people who do develop complicated influenza are likely to be more difficult to treat or die.

Health care workers are generally considered to be a priority vaccination group. They may become infected either by exposure to influenza in the community or in their place of work, and they have been shown to transmit infection to other staff members and those they care for, who are themselves in a risk group for complications. A substantial number of HCWs become infected during the influenza season and some continue to work even with symptoms of influenza, potentially increasing the possibility of transmission to those in their care. There is low-quality evidence that vaccinating HCWs has a small protective effect against ILI and all-cause mortality for people in their care who live in LTCFs (Annex C2). Low vaccination coverage among HCWs has made it difficult to

assess the true impact of vaccination and reasons for non-vaccination should be addressed in order to improve coverage, to allow further evaluation of this intervention and add to the current evidence base.

There is evidence from RCTs and observational studies that pneumococcal vaccination offers protection against invasive pneumococcal disease in healthy adults (Annex C3), although it is unclear from the evidence from RCTs whether the vaccine is as efficacious in those with chronic disease. Data from observational studies indicates that there may be an additive effect of influenza and pneumococcal vaccines in reducing the risk of complications of influenza.

Surveillance

- All staff should be aware of the early signs and symptoms of influenza-like illness, and alert for groups of residents becoming ill simultaneously or in short succession.
- Surveillance for influenza should be done throughout the year but particularly between October to the end of May (the influenza season in the Northern Hemisphere).
- The management should be aware of influenza activity in the local community.
- There should be set definitions and escalation/notification procedures for recognition of potential influenza outbreaks, bearing in mind that visiting health care staff (e.g. GPs) may only attend to provide care for a single resident and will therefore potentially miss a common illness syndrome seen in multiple residents. Attending GPs should therefore inform a senior staff member as soon as possible if they attend a resident with influenza-like illness or other symptoms suggestive of influenza.
- Surveillance of clusters of cases with severe illness may help to identify high threat respiratory pathogens, such as avian or pandemic influenza, or MERS-CoV.

Rationale:

Outbreaks of influenza may occur in LTCFs at any time of year, not only during the influenza season and all staff should be aware of this so that prompt control action can be instigated. Often the first signs of an approaching influenza season in the wider community are outbreaks in semi-closed settings.

Early recognition of a potential outbreak

Case definition of influenza-like illness

Seasonal influenza is characterized by sudden onset of fever, cough, headache, muscle and joint pain, severe malaise, sore throat and runny nose. Point-of-care (POC) rapid tests (near-patient tests (NPTs) may be a useful adjunct but **due to low sensitivity a negative POC test does not rule out influenza**. Laboratory diagnosis is required to confirm a clinical or suspected diagnosis of influenza, and for confirmation of any POC tests undertaken. The precise definition of influenza-like illness may vary from country to country, but the WHO global surveillance case definition of ILI is of an acute respiratory infection with measured fever ≥38°C and cough and onset within the last 10 days (3). Severe acute respiratory infection (SARI) is also defined by these features but requires hospitalization (3). The EU definition of ILI is sudden onset of symptoms and at least one of four systematic symptoms (fever or feverishness, malaise, headache, myalgia) and at least one of three respiratory symptoms (cough, sore throat, shortness of breath)(4). **However, it is important to note that in the elderly, the presentation may be atypical and with lack of fever. Influenza may present as sudden, unexplained deterioration in physical or mental ability or exacerbation of an underlying condition with no other known cause. The use of the WHO surveillance case definition for ILI and SARI in these populations may miss cases, especially if they present without fever. Staff should be encouraged to seek diagnostic investigation of individuals suspected of having influenza regardless of the case definition in an effort to pick up cases early in their illness in order to prevent the spread of infection.**

One case may be indicative of other cases in exposed persons (residents and staff); these should be actively sought through temperature monitoring and symptom review.

Outbreak definition

Action threshold for implementing outbreak control measures:

The occurrence within 48 hours of two or more cases of ILI, or probable or possible influenza, or laboratory confirmed influenza with an epidemiological link

Or

The occurrence within 72 hours of three or more cases of ILI, or probable or possible influenza, or laboratory confirmed influenza with an epidemiological link.

Possible cases: meeting the defined clinical criteria

Probable cases: meeting the clinical criteria and having an epidemiological link to a confirmed case.

Confirmed cases: meeting the clinical criteria, having an epidemiological link and confirmation.

Notification of a suspected outbreak

- Staff working within the facility should be aware of their upward notification chain, whereby possible cases are notified to senior members of staff to ensure that appropriate actions are taken.
- If a possible outbreak of influenza is suspected based on the above case definitions, the attending medical team/GP should be immediately informed for assessment and diagnosis.
- The GP providing medical care to the facility should then notify the on-call Public Health specialist for further advice on testing and management.

Public health authorities

- Local public health (health protection) units should ensure that appropriate measures are in place to raise awareness among LTCFs and GPs of the importance of them reporting suspected outbreaks to the local public health authority at an early stage.
- Locally appropriate arrangements should be in place to facilitate reporting and sampling.
- Local public health (health protection) units should liaise with local microbiology/virology laboratories to coordinate taking diagnostic samples from symptomatic residents as soon as possible.
- Investigation protocols should be in place that have been agreed with the local microbiologist/virologist, including provision for the transfer of specimens to regional or national laboratories if required.

Testing for influenza

- The management of LTCFs should be aware of local arrangements that are in place to obtain respiratory tract samples for virology, and who is responsible for taking specimens (this may also vary regionally).
- Specimens for testing for influenza should be taken with advice from the local public health (health protection) unit. Other respiratory virus pathogens which may cause acute respiratory illness should be considered and tested for based on advice from local public health authorities.

- Respiratory samples (nose, throat or nasopharyngeal swabs) should be taken as soon as possible from symptomatic residents (preferably within 48 hours of symptom onset), prioritizing those with most recent symptom onset. The number of residents swabbed will depend upon the needs of the facility.
- To confirm an outbreak, RT-PCR is the preferable method of laboratory testing, including typing/subtyping. Rapid POC ('bedside' or near-patient) tests are not as sensitive but can be useful in outbreak situations, for example for rapid identification of influenza infection where timely access to more sensitive and specific laboratory testing is unavailable or delayed. However, bear in mind that health care workers should use clinical judgement to interpret negative test results for individual patients during an outbreak.
- Additional testing, requiring viral culture, may be needed if there are unusual cases and clusters of disease.
- Other respiratory virus pathogens which may cause acute respiratory illness should be considered and tested for where appropriate and in the absence of influenza virus.

Outbreak measures

Initial actions

- Start general outbreak control measures as soon as possible and before virological confirmation. Note that a negative near- patient or bedside test does not exclude influenza because sensitivity is suboptimal and should be confirmed by the laboratory. See Annex A8 for an outbreak management flowchart.
    - Apply Standard Precautions routinely to ALL patients in ALL health-care settings.
    - Apply Standard and Droplet Precautions at the initial evaluation of a patient with a suspected ILI. Modify isolation precautions according to the specific diagnosis, as it becomes available.
    - Apply Standard, Contact and Droplet Precautions at initial evaluation of a paediatric patient presenting with a suspected ARI during the peak season of certain viruses (e.g. croup and parainfluenza, acute bronchiolitis, and respiratory syncytial virus). Modify isolation precautions according to the specific diagnosis.
    - Evaluate the risk to determine whether additional protective measures may be necessary; for example, when providing care for patients infected with some specific pathogens. If the patient has indications suggestive of a novel ARI with epidemic or

pandemic potential and the route of transmission has not been established, add Airborne and Contact Precautions, plus eye protection, to Standard Precautions. Consider the use of patient cohorting – that is, place patients infected or colonized with the same laboratory-confirmed pathogens in the same designated unit, zone or ward (with or without the same staff) – to reduce transmission of ARI pathogens to health-care workers and other patients.

- When there is no laboratory confirmation, apply special measures – that is, place patients with the same suspected diagnosis (similar epidemiological and clinical information) in the same designated unit, zone or ward (with or without the same staff) – to reduce transmission of ARI pathogens to health-care workers and other patients.
- Avoid sharing of equipment. If sharing is unavoidable, ensure that reusable equipment is appropriately disinfected between patients.
- Encourage the use of medical masks by patients with ARI during transport or when care is necessary outside of the isolation room or area. If medical masks are not available or not tolerated by the patient, other methods to reduce the dispersal of respiratory secretions, including covering the mouth and nose with a tissue or flexed elbow during coughing or sneezing, can be used, and should be followed by hand hygiene. For more information on respiratory hygiene, see Annex A.

- The LTCF lead person should draw up a daily case list of affected residents and staff and communicate this to the local health protection unit.
- Undertake active daily surveillance with daily temperature measurement of all residents and staff and review of possible symptoms to identify new cases.
- Staff and residents who have not received the current seasonal influenza vaccine before the outbreak, should be offered vaccination as soon as possible after identification of an outbreak if it is not contra-indicated. However, this is an opportunistic process and **should not be considered as a control measure or as an alternative to control measures, as approximately 14 days will be required for seroprotection to develop.**
- Consider antiviral prophylaxis for those who have already been exposed who have high-risk conditions.

Public health authorities

Local public health (health protection) units should have a local outbreak plan in place.

Upon notification of a suspected outbreak in a LTCF, a risk assessment should be undertaken to verify the extent and severity of the outbreak, taking into account the following:

- the number of ill residents and total
- the number of ill staff and total
- visitors and relatives with similar illness
- layout of the LTCF
- infection control measures that are already in place
- test results from clinical specimens that have been taken (and swabs for other pathogens)
- vaccination status of residents and staff
- antivirals that have been started for treatment or chemoprophylaxis
- current levels of circulating influenza in the community

The decision should then be made whether it is necessary to convene an outbreak control team (OCT).

If the decision is taken not to convene an OCT, the local Public Health Authority will continue to provide advice and support to the LTCF on further management of the outbreak including advice on the use of transmission-based precautions, vaccination and antiviral treatment and prophylaxis.

The Outbreak Control Team

Membership of the OCT will depend upon the availability of expertise, and prevailing national and local arrangements/provision, but may include the following:

- Public Health Specialist
- Medical representative from the LTCF
- Management representative from the LTCF
- Nursing representative from the LTCF
- Consultant microbiologist/virologist
- Public Health Laboratory *representative/National virus reference laboratory* representative
- Infection control nurse
- Occupational Health Physician
- Pharmacist
- Administrative support
- Communications/Press officer

The OCT will help to coordinate active case finding and testing, prepare communications for staff, residents and family members, agree infection control measures (including antiviral treatment and prophylaxis), review staffing contingency plans, provide updates to the Director of Public Health if required, and prepare a media release if appropriate.

Infection prevention and control guiding principles

The principles of IPC for managing outbreaks of Influenza in LTCF include:

• early and rapid recognition of patients;

• application of routine IPC precautions (Standard Precautions) for all patients;

• additional precautions in selected patients (e.g. based on the presumptive diagnosis);

• establishment of an IPC infrastructure for the health-care facility, to support IPC activities.

IPC strategies in health-care facilities are commonly based on early recognition and source control, administrative controls, environmental and engineering controls, and personal protective equipment (PPE).

Detailed information on infection prevention and control precautions may be found in the WHO guidelines 'Infection prevention and control of epidemic– and pandemic–prone acute respiratory infections in health care' (http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf?ua=1). Additional information on IPC in health care facilities and LTCFs is also available from the Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (5-7). The principles which are relevant to the LTCF setting are outlined here.

Standard precautions

Standard precautions are a basic set of precautions or routine measures that should be practiced at all times by all staff with all residents and their importance should be reinforced during an outbreak. The key components of standard IPC precautions are hand hygiene, use of PPE, respiratory hygiene, environmental control (cleaning and disinfection), waste management, packing and transporting of patient–care equipment, linen and laundry and waste from isolation areas, and the prevention of needlestick or sharps injuries.

Transmission-based precautions

Transmission-based precautions are a set of infection prevention and control measures that should be implemented when residents are known or suspected to be infected, and include contact, droplet and airborne precautions. They should be used as required whilst ensuring that standard precautions are maintained.

Contact Precautions

Contact precautions are taken to prevent the transmission of pathogens from a patient or their environment to an uninfected host, particularly through hand contamination and self-inoculation of the conjunctival or nasal mucosa. The use of PPE, environmental control measures, and patient placement and transport are the key elements of contact precautions.

Droplet Precautions

Droplet precautions are intended to prevent transmission of pathogens through close respiratory or mucous membrane contact with respiratory secretions, and should be practiced in addition to standard precautions. They include patient placement, use of a medical mask when working within 1-2 meters of patients, and use of a medical mask by patients when being transported. These precautions are outlined further below.

Airborne Precautions

Airborne Precautions offer protection against the transmission of airborne pathogens contained in droplet nuclei which remain infectious whilst suspended in the air. The use of PPE, (including a particulate respirator for staff performing or being exposed to residents requiring tracheal or complex airway care), patient placement, and limiting patient movement within the facility with use of a medical mask worn by the patient if this cannot be avoided, are additional precautions to be used as supplement to Standard Precautions.

Placement of affected residents

- Symptomatic residents should be cared for in their own, preferably single occupancy, rooms until fully recovered.
- Encourage residents to stay in their room with the door closed (a safety/welfare assessment may be necessary for some residents). Place an appropriate sign on the door to identify areas where residents are being isolated or cohorted.
- Meals should be taken within their rooms to avoid mixing with other residents in communal

areas.

- If isolation is not possible, cohort symptomatic residents away from those who remain well, with separate cohorts of suspected and confirmed influenza cases.
- Staff assignment – assign certain staff (preferably vaccinated) to work only with symptomatic residents and in contaminated areas OR to work only in asymptomatic and non-contaminated areas. Do not mix staff between the two types of patients or between areas until the outbreak is over.

Rationale:

Physical separation of residents or cohorting residents infected with influenza in the same unit or zone and minimising staff movements between affected and unaffected areas can reduce transmission of virus to other residents and staff and facilitate the application of IPC measures. HCWs and other staff members can become infected through exposure to infected residents, and once infected they become a source of transmission to other staff and uninfected residents in their care. The allocation of vaccinated staff to care for infected residents may therefore reduce the risk of transmission from HCW to vulnerable uninfected residents.

Respiratory hygiene and etiquette

- Residents and staff should cover their nose and mouth when coughing or sneezing using tissues, masks or flexed elbow in order to contain respiratory secretions, followed by hand hygiene.
- The management should promote the practice of respiratory etiquette for staff, residents and visitors and should ensure that there are adequate hand- washing facilities and disinfectant hand rubs where sinks are not available.
- Adequate supplies of tissues, covered sputum pots and no-touch bins for disposal of soiled tissues should be made available.
- When a symptomatic resident needs to be moved outside their room or cohort area, consideration should be given to them wearing a medical mask if they are able to tolerate this.

Rationale:

Respiratory hygiene is a source control measure intended to contain respiratory secretions in order to prevent the transmission of respiratory pathogens in the environment. Limited experimental evidence indicates that although covering the mouth and nose with a tissue or medical mask during

coughing and sneezing may not completely contain respiratory droplets, their dispersal is reduced and it is preferable to unobstructed coughing and sneezing (8, 9). Hand hygiene can reduce the spread of respiratory viruses and can be extrapolated to respiratory hygiene as a potential way of limiting contact transmission of virus from hands contaminated with respiratory secretions.

Hand Hygiene

Hand hygiene practices for HCWs should be performed at five critical points during patient care:

1) before touching a patient

2) before a clean/aseptic procedure

3) after a procedure or body fluid exposure risk

4) after touching a patient

5) after touching the patient's surroundings

Even when gloves are worn, hand hygiene should be performed immediately after gloves are removed. Employees who may not necessarily have direct patient contact should also practice hand hygiene if appropriate e.g. after cleaning communal areas and during food preparation.

- When the hands are visibly soiled, or when broken skin may have been contaminated by body fluids, wash them thoroughly using liquid soap and water and dry well with a disposable paper towel or single use towel.
- When hands are not visibly soiled an alcohol-based handrub may be used.

Rationale:

Hand hygiene is a key element of Standard Precautions which is easy to perform and has been shown to be effective in the preventing and controlling the spread of infection in health care facilities. Failure of HCWs to properly clean hands between patient contacts or during the sequence of patient care, can result in microbial transfer and cross–contamination. There is good evidence that frequent handwashing with or without adjunct antiseptics is an effective way of reducing the transmission of respiratory viruses, although the evidence does not relate specifically to influenza virus or to the LTCF setting (10) (Annex C5). For laboratory-confirmed influenza, there is evidence that hand hygiene plus use of medical masks is effective at preventing infection, although hand hygiene on its own has not been shown to significantly reduce influenza illness (11) (Annex C4). Compliance with recommended hand hygiene procedures is often inadequate which may in part help to explain this apparent lack of efficacy of hand hygiene alone. A combination of correctly

performed hand hygiene in addition to other measures that protect against other modes of transmission of influenza is likely to be important in reducing influenza transmission.

Alcohol-based handrubs are recommended by the WHO for hand hygiene when hands are not visibly soiled, based on their broad-spectrum microbiocidal activity, potential to promote compliance with hand hygiene practice, economic benefit, and safety profile. They are generally acceptable, well-tolerated and suitable for use in resource poor settings (full information about hand hygiene guidance may be found in the 'WHO guidelines on hand hygiene in health care' available at http://www.who.int/gpsc/5may/tools/9789241597906/en/). As alcohol-based handrubs do not have detergent properties, they should not be used when the hands are visibly soiled, in which case they should be thoroughly washed with soap and water.

Use of Personal Protective Equipment

The selection of appropriate PPE will be determined by risk assessment according to the procedure to be performed and anticipated risk of exposure to infectious material. Whenever possible, single use disposable PPE items should be used, or if this is not possible, reusable items such as disinfectable cotton gowns should be disinfected thoroughly after each use.

PPE should be donned upon entering an affected resident's room or cohort nursing area, and removed and disposed of immediately prior to leaving the room or area. As viruses may be transferred to the hands during removal of PPE, it must always be followed by hand hygiene.

Staff should be trained to use PPE correctly and to practice hand hygiene effectively.

Gloves

- Gloves should be worn when contact with blood, body fluids, mucous membranes or non-intact skin is anticipated.
- Carefully remove gloves after use and before touching non-contaminated surfaces and items, and before caring for another resident.
- Wearing disposable gloves is not a substitute for hand hygiene and hand hygiene must always be performed immediately after removal of gloves.

Gowns and aprons

- Gowns should be worn when contact is anticipated with splashes or sprays of blood, body fluids, secretions and excretions.

- If the gown is not fluid resistant, a disposable plastic apron should also be worn when contact with splashes or sprays of potentially infectious material is anticipated.
- Soiled gowns and aprons should be removed as soon as possible and disposed of in a waste or laundry receptacle.
- When residents are cohorted, gowns may be worn for the care of more than one resident in the same cohort area, provided that it does not come into direct contact with the resident.
- Perform hand hygiene after removal of gowns and aprons.

Facial Protection

- Medical masks should be worn closely fitting to the face and changed immediately when soiled with secretions or becoming moist.
- Eye protection (goggles or shield) should be worn to protect the conjunctivae and mucous membranes when providing close contact care to residents with respiratory symptoms such as coughing or sneezing. To avoid risk of cross-infection, reusable eye protection should be cleaned and disinfected according to manufacturer's instructions after each use.
- Cloth or gauze masks should NOT be used as their moisture retention properties are associated with poor filtration and reuse may increase the risk of infection.
- A mask should be worn by infected residents if it is necessary to move them out of their room.

Rationale:

There is weak evidence that the use of PPE has a consistent, although non-significant protective effect in reducing influenza-like illness attack rates in LTCFs (12). Low quality evidence from a small number of observational studies has indicated the effectiveness of individual interventions in reducing the spread of influenza (10)(Annex C5). There are few data that support the use of masks or respirators to prevent infection in the wearer. However, there is some evidence that masks may reduce infectiousness if worn by an infected person, thus justifying their use when movement of infected residents outside their room is necessary (13, 14)(Annex C4). Although there is some evidence to suggest that fitted respirators may have a protective advantage over medical masks in the laboratory setting, the data are insufficient to determine whether respirators are superior to masks in the clinical setting.

As there are still uncertainties about the relative contributions of the different modes of transmission of influenza (contact, droplet and aerosol) it is prudent to combine non-pharmaceutical interventions as part of good clinical infection control practice.

PPE is meant to provide additional protection to the user, but if used incorrectly may increase risk of transmission of pathogens to other users or transfer into the environment. Particular care should be taken when removing PPE and it should always be followed with hand hygiene (15). Correct usage and compliance with hand hygiene and the use of PPE will enhance their effectiveness.

Aerosol Generating Procedures

When carrying out an aerosol generating procedure (AGP) associated with increased risk of transmission of airborne pathogens (tracheal intubation, non-invasive ventilation, tracheostomy, manual ventilation before ventilation), select the highest level of respiratory protection available and ideally a particulate respirator (FFP2 or FFP3/N95 or N99). Staff wearing particulate respirators will need to be formally fit-tested prior to their initial use, and fit-checked thereafter.

- Check the seal of the respirator when putting it on.
- Change respirator after each use or if it becomes wet or dirty.
- Wear gloves, gown and eye protection.
- Perform the procedure in a well-ventilated room.
- Limit the number of people in the room to the absolute minimum required for care of the resident.
- Perform hand hygiene before and after contact with the resident and their surroundings and after removal of PPE.

Rationale:

For AGPs, there is evidence from SARS-CoV infections of a consistent association between pathogen transmission from the infected patient to staff when the patient is undergoing tracheal intubation. A few studies have reported increased risk of transmission from infected patients undergoing other AGPs, notably tracheostomy, non-invasive ventilation and manual ventilation before intubation, but interpretation of these results is difficult and based on low quality evidence (16). No other procedures, including suction, nebuliser treatment, oxygen administration, chest compression, defibrillation, nasogastric tube insertion or chest physiotherapy, were found to be associated with a significantly increased risk of transmission of ARIs to HCWs. Information has been provided here on precautions for AGPs, as although high-risk procedures are unlikely to be performed in LTCFs caring largely for elderly residents, it is possible that some LTCFs with a different resident profile (e.g. rehabilitation facilities for the disabled) may have a requirement for AGPs as part of routine care.

Environmental Control Measures

A range of chemical disinfectants is available and should be used in accordance with the manufacturer's instructions as well as national and local policies on the use of these disinfectants. There is evidence that simple, readily available and easy to handle products such as disinfectants like 1% bleach, 10% vinegar and detergents like 0.01% washing-up liquid (containing ionic detergents and non–ionic detergents) are effective at killing influenza virus depending on the situation and material to be disinfected and can be used in low resource settings (17); complex disinfection agents are not required to inactivate human influenza viruses. Manufacturers' instructions should be followed regarding the preparation of disinfectants, use, contact time required and handling precautions, and appropriate PPE should be worn to protect the user.

Resident environment

- Clean surfaces and equipment that come into direct contact with residents thoroughly after use.
- Clean resident rooms daily with particular emphasis and more frequent cleaning of horizontal surfaces, frequently touched surfaces (e.g. bedside tables, door handles, alarm buttons) and in the immediate vicinity surrounding the resident's bed.
- Clean frequently touched surfaces in communal areas (e.g. door handles, hand rails) at least twice a day.
- Surfaces or items which are visibly contaminated should be cleaned immediately.
- Clean items and surfaces prior to disinfection as disinfection will not be effective in the presence of organic matter.
- Avoid dry dusting and sweeping to minimise the potential generation of aerosols.
- Keep resident rooms clutter free and avoid stockpiling of equipment.
- Avoid the use of fans.
- If reusable mop heads are used, they should be laundered daily and dried thoroughly prior to re-use.

Equipment used in resident-care

- Clean, disinfect and sterilise (where appropriate) reusable equipment according to manufacturers' instruction and local policies.

Laundry

- Contaminated linen should be placed into a laundry bag in the isolation room or cohort area.

- Handle laundry as per the facility's protocol for dirty linen using a proprietary washing detergent.

Eating utensils and crockery

- When possible wash reusable eating items in a dishwasher.
- Alternatively dishes may be washed by hand using detergent and hot water and using non-disposable rubber gloves.

Rationale:

Influenza virus can survive in the environment for variable periods of time. Direct and indirect contact are potential routes of transmission for influenza (18, 19). Cleaning reduces the bio-burden of microorganisms on contaminated surfaces and standard disinfectants inactivate them.

Containment Measures

Containment measures aim to limit contact between infected or potentially infected people and susceptible individuals, thus limiting transmission contact networks.

New admissions to LTCF

- Closure to new admissions to the LTCF (or part of the LTCF) should be based on a risk assessment of the feasibility of establishing self-contained areas for symptomatic residents and the staff caring for them. This decision should be taken upon advice from the local health protection or the OCT if this has been convened, who will also advise on the duration of closure.

Transfers to hospital or other LTCF

- Transfers to other health care facilities from LTCFs experiencing an outbreak of influenza should only be done when clinically necessary and the facility is unable to provide adequate care for that person.
- The transportation company and receiving facility should be warned in advance of the transfer and have written notification of this to ensure that correct infection control measures are in place when transporting and receiving the resident.

Discharge of patients from hospital back to a LTCF

- A careful risk assessment with involvement of the health protection unit or OCT should be carried out before residents who have been in hospital are discharged back to a LTCF experiencing an influenza outbreak.
- Residents who had a diagnosis of influenza may be discharged back to the LTCF provided the following conditions are met:
    - Isolation is continued whilst the resident remains symptomatic (or longer if the resident has a major medical condition, immune suppression, had pneumonia, antivirals were started more than 48 hours after onset, no antiviral treatment was given, or if respiratory symptoms persist beyond 5 days).
    - The causative strain is the same as that in the LTCF.
- Readmission to the LTCF of residents who were admitted for reasons other than influenza should generally be delayed.

Restriction of communal activities

- Internal communal activities for residents should be restricted and attendance at external social activities and non-urgent medical appointments curtailed or cancelled.
- If possible measures should be taken to discourage congregation of residents e.g. extending mealtimes, reducing the number of residents in one area at any one time.
- Social distancing and isolation may have a negative psychosocial impact on residents, resulting in impaired quality of life and deterioration of functional status. Staff should be aware of this and aim to minimise residents' psychological distress as much as possible.

Staffing precautions

- Whenever possible, staff should care for either affected residents or uninfected residents, but not both.
- If possible, vaccinated staff should care for infected residents.
- Unvaccinated staff in a risk group for complications (e.g. pregnant women or if immune suppressed) should avoid caring for infected residents.
- Staff members with fever or symptoms of influenza should be excluded from work for at least 5 days after symptom onset, preferably until recovered.
- Temporary and agency staff may work in other health care facilities if they have been vaccinated and are asymptomatic.

- Unvaccinated, asymptomatic staff (including agency staff) who have been in contact with symptomatic residents should avoid working in other non-outbreak facilities (e.g. the local hospital or a neighbouring LTCF) until the outbreak is declared over.

Visitor Restrictions

- Limit to regular visitors as much as possible (although this needs to be weighed against the psychological and compassionate benefits to the residents).
- Exclude visitors with symptoms of influenza, and also those at high-risk of developing complications including young children and pregnant women.
- Signs should be placed at the entrance to the facility indicating that there is an outbreak, either within the facility itself or in the case of a local or regional outbreak, listing the precautions to be taken and advising visitors with symptoms to stay away from the facility.
- Restrict visits to one resident, and encourage them to leave the facility as soon as possible after their visit.
- Advise visitors on the appropriate use of hand hygiene, including hand-washing or use of an alcohol-based hand rub on entering and leaving the facility.
- Encourage visitors to minimize their direct contact with residents, follow hand hygiene and cough etiquette and to use PPE appropriate to the degree of contact anticipated and the risk of exposure to infectious material if visiting an infected resident.

Use of Antivirals

Antiviral treatment

- Given the high-risk of severe complications and deaths among the elderly from influenza virus infection, and the abruptive nature and devastating consequence of institutional outbreaks, where influenza antivirals are available, treatment of symptomatic LTCF residents should be started immediately without delay. Where antivirals are not available, a good supportive care and careful patient monitoring for signs of secondary bacterial infection e.g. bacterial pneumonia should be conducted. Bacterial pneumonia should be timely treated by the first-line antimicrobials considering the local susceptibility profile of the common CAP pathogens.
- Treatment should be started as soon as possible after the onset of symptoms regardless of vaccine status and should not wait until laboratory confirmation. Early treatment with

neuraminidase inhibitors (NAI) may reduce mortality when started within 48 hours of symptom onset in those with severe influenza requiring hospital admission.

Rationale:

There is a paucity of evidence available to guide clinicians on antiviral treatment of people in high-risk groups, including the elderly and those living in LTCFs, so decisions need to be based on clinical judgement and outbreak severity (20). A recent ECDC expert opinion on the use of antivirals for treatment recommends treating long-term care residents during seasonal influenza epidemics, based on a risk assessment, and advises that lack of evidence from clinical trials should not prevent treatment when clinically indicated (21).

Although treatment may lead to a reduction in the time to alleviation of symptoms, this effect is only modest (a few hours), and appears to be attenuated in the elderly (Annex C6). Time to symptom reduction may not be an outcome of importance to LTCF residents, although it may decrease the potential for complications to arise. There is a lack of credible evidence that the NAIs reduce the risk of pneumonia (although findings between trials are difficult to compare due to lack of standardization of the definition of pneumonia with some trials including self-reported pneumonia as an outcome rather than radiological or clinician diagnosed pneumonia). Treatment trials of NAIs were generally underpowered to evaluate the effects of treatment on complications due to the rarity of such events in participants (who were generally previously healthy younger adults rather than frail elderly residents of LTCFs). Evidence from the Post-pandemic Review of anti-Influenza Effectiveness (PRIDE) study) showed that deaths were reduced in hospitalised patients when treated with NAIs within 48 hours of onset, supporting the use of early NAI treatment in those who require hospitalization (22). Reduced mortality was also found in a meta-analysis of 3 observational studies, but the quality of evidence was low, and related only to oseltamivir, not zanamivir. Patients treated with oseltamivir have significantly increased risk of nausea and vomiting (number needed to harm, i.e. the number of people who would need to receive the drug for one person to experience the adverse effect, =28 and 22 respectively), although zanamivir was not associated with increased rates of reported adverse events. Adverse events may be more common in the elderly, but there are no studies that address this.

Antiviral prophylaxis

- For asymptomatic LTCF residents, the decision to give prophylaxis during a seasonal influenza outbreak should be made on an individual basis using clinical judgement and based on the underlying medical conditions and risk of exposure. For example, a fully bed ridden

resident with chronic lung obstructive disease in the same room as a patient presenting with ILI is likely to benefit from antiviral prophylaxis (post-exposure prophylaxis) regardless of vaccination status. Even when the vaccine strains and circulating strains are well matched, vaccine effectiveness is lower in the elderly than in younger age groups.

- If used for post-exposure prophylaxis, it should be commenced as soon as possible due to the short incubation period and may be continued up to 10 days after the most recent exposure to a confirmed case.
- Prophylaxis of HCWs working in the facility (irrespective of vaccination history), is not generally recommended but might need to be considered if there is epidemiological and/or virological evidence of ongoing chains of transmission involving residents and staff. Institute a health monitoring of HCWs and advise those with presenting relevant symptoms to stay home and not attend.
- Prophylaxis should be discontinued if a causative agent other than influenza is identified.
- Consider the possibility of antiviral resistant virus in those who become ill after starting prophylaxis. Carefully exclude non-compliance. Naso-pharyngeal, throat or nasal swabs from additional symptomatic people should be taken when new influenza-like cases arise 72 hours or more after the instigation of antiviral chemoprophylaxis to check for the emergence of a resistant strain.
- Locally agreed arrangements for pre-ordering antiviral drugs (e.g. with pharmacists) will expedite their provision and facilitate early administration.

Rationale:

There is a lack of evidence from recent studies to inform a single approach for antiviral prophylaxis use in LTCFs, so decisions should be based on clinical judgement and outbreak severity, although this information may not be available until later on (20). A recent ECDC expert opinion on the use of antivirals for prophylaxis recommends consideration of antiviral prophylaxis for residents of LTCFs, especially for those who are unvaccinated or immunocompromised who do not respond to vaccination(21). This may be particularly important during years when vaccine effectiveness is expected to be low due to vaccine strain mismatch, although early in the influenza season this information may not be available. The relatively low effectiveness of influenza vaccine in the elderly population should also be taken into consideration.

Prophylaxis with NAIs has been shown to be more effective than placebo at preventing symptomatic influenza in individuals and household contacts in RCTs (23)(Annex C7), and supported by additional data from observational studies (24). However, direct evidence of effectiveness in reducing

symptomatic influenza in the frail elderly living in institutions is sparse; a non-significant protective trend with post-exposure zanamivir prophylaxis has been shown in one study but there are no data for the effectiveness of post-exposure oseltamivir in this group (25). The use of oseltamivir has been shown to increase the risk of headaches, nausea and psychiatric events in trial participants, who are often healthy adults (NNTH 32, 25 and 94 respectively)(23). Many residents of LTCFs will have other co-morbidities which may affect the number of unwanted side effects in this group. There are no studies that have evaluated the effectiveness of giving prophylaxis to health care workers, but as the majority of HCWs are likely to be healthy adults, they may benefit from a protective effect, not only on a personal level but which may also protect those in their care and benefit the facility by decreasing staff absenteeism during the outbreak.

Recommended doses of NAIs when used for treatment and post-exposure prophylaxis

Oseltamivir

Treatment of influenza

For adolescents (13-17 years) and adults, the recommended oral dose is 75mg twice daily for 5 days(26, 27). No dosage adjustment is required for the elderly unless there is evidence of moderate or severe renal impairment (Table 1). Treatment should be commenced as soon as possible and preferably within the first two days from onset of symptoms.

Table 1. Oseltamivir dose recommendations in renal impairment for treatment of influenza

Creatinine clearance	Recommended oseltamivir dose for treatment of influenza
>60 ml/min	75 mg twice daily
>30 to 60 ml/min	30 mg (suspension or capsules) twice daily
>10 to 30 ml/min	30 mg (suspension or capsules) once daily
≤10 ml/min	Not recommended
Haemodialysis	30 mg after each haemodialysis session
Peritoneal dialysis	30 mg (suspension or capsules) single dose

Post-exposure prophylaxis of influenza

For adolescents (13-17 years) and adults, the recommended oral dose is 75mg once a day for 10 days(26, 27). No dosage adjustment is required for the elderly unless there is evidence of moderate or severe renal impairment (Table 2). Oseltamivir should be commenced as soon as possible within two days of exposure.

Table 2. Oseltamivir dose recommendations in renal impairment for prevention of influenza

Creatinine clearance	Recommended oseltamivir dose for prevention of influenza
>60 ml/min	75 mg once daily
>30 to 60 ml/min	30 mg (suspension or capsules) once daily
>10 to 30 ml/min	30 mg (suspension or capsules) every second day
≤10 ml/min	Not recommended
Haemodialysis	30 mg after every second haemodialysis session
Peritoneal dialysis	30 mg (suspension or capsules) once weekly

Zanamivir

The recommended dose of zanamivir for the treatment of influenza in children aged ≥5 years and adults is two inhalations (2 x 5 mg) twice daily for five days (28). No dosage amendment is required in the elderly or in people with renal impairment.

End of outbreak

- Advice should be sought from the public health (health protection) unit or OCT on when the outbreak can be declared over based on an ongoing risk assessment of the situation (usually this will be about eight days after the onset of symptoms in the final resident case, based upon a period of communicability plus one incubation period (29)).
- Representatives of the LTCF should meet with public health within a defined time period after the end of the outbreak to review the management of the outbreak, consider lessons learned and review and modify risk mitigation strategies where necessary.

Summary table

	Domain	Action	Comment
Pre-outbreak Measures	Planning and administration	Written policies	Immunization policies. Standard and Transmission based precautions. Written outbreak management plan.
		LTCF Lead (named person)	To oversee development, implementation and review of policies and protocols.
		Training and education	For all staff. Ongoing training. Measures to improve compliance.
		Provision of supplies	Hand hygiene supplies, PPE, cleaning and disinfecting material. Arrangements with pharmacy for supply and timely provision of antivirals.

	Vaccination of residents	Influenza vaccination – residents	Offer to all residents prior to season. Offer catch-up vaccination to new unvaccinated residents. Document in care records.
		Pneumococcal vaccination	Offer to previously unvaccinated residents.
	Vaccination of staff	Influenza vaccination – staff	Maximize uptake prior to influenza season. Named staff member responsible for coordination. Record vaccination status in staff records. Feedback on vaccination coverage.
	Standard Precautions	Standard Infection control procedures	Should be practised by all staff at all times.
	Surveillance	Awareness of influenza signs and symptoms	Throughout the year but particularly October to May.
Early recognition	Case definition	Case definition	In the elderly presentation may be atypical and without fever.

	Outbreak definition	Action threshold for outbreak control measures	≥2 epidemiologically-linked cases within 48 hrs OR ≥3 epidemiologically-linked cases within 72 hours.
	Communication of suspected outbreak	Notification of senior staff, management, medical staff, public health	Staff to be aware of upward notification chain. Contact GP/medical team. Notify Public Health locally.
	Formation of OCT	OCT may be convened following risk assessment	Coordination with Public Health locally.
	Testing	Viral swabbing	Awareness of local provision of viral swabs and authority responsible for taking samples. Coordination with Public health and local laboratory.
During an outbreak	Initial actions	Daily case list	Daily list of affected residents and staff communicated to public health.
		Active daily surveillance	Daily temperature and symptom review of residents and staff to identify new cases.

		Vaccination	Offer to unvaccinated residents and staff (but not as a control measure)
	Infection Control Measures	Standard and transmission-based precautions	Standard precautions should be in place already but heightened. Transmission-based precautions (droplet, airborne and contact) should be implemented as appropriate.
		Resident Placement	Single room isolation/Cohorting
		Respiratory hygiene	Cover mouth and nose for coughing/sneezing. Adequate supplies of tissues and disposal bins. Hand hygiene after respiratory hygiene. Masks for residents transported out of isolation area.
		Hand Hygiene	5 critical points in resident care. Hand hygiene after PPE removal.
		Personal protective equipment	Gloves, aprons, gowns, face protection.
		Aerosol generating procedures	Highest level of respiratory protection (FFP2/3)

			available if performing a high-risk AGP.
		Environmental control measures	Resident environment cleaning and disinfection. Resident care equipment. Laundry. Eating utensils and crockery.
		Containment measures	New admissions restricted. Transfers restricted. Discharges of residents back to LTCF from hospital, depending upon whether diagnosed with influenza or not. Restricted communal activities. Staffing precautions. Visitor restrictions.
	Use of Antivirals	Treatment	Recommended on an individual basis taking into account the balance of risks and benefits.
		Prophylaxis	Decision for residents based on risk assessment, clinical judgement and outbreak severity.

			Consider for HCWs if unvaccinated and in seasons when vaccine mismatched with circulating strain; and where evidence exists for complex ongoing chains of transmission involving patients and staff.
Post outbreak	Declaration of end of outbreak		As advised by Public Health
	Final evaluation	Review of management of outbreak and lessons learned.	Coordination with Public Health and OBCT if this was convened.

ANNEXES

Annex A – Work-aids

A1: Guidance poster for use by LTCF

A2: Day 0 actions checklist

A3: Daily actions checklist

A4: Outbreak line listing form – residents

A5: Outbreak line listing form – staff

A6: Daily update reporting form

A7: End of outbreak summary report

A8: Outbreak management flowchart

A9: Inter-facility transfer form

A10: WHO hand hygiene leaflet

A11: WHO personal protective equipment leaflet

A12: Door sign

A13: Visitor poster

Annex B – Literature review

The population at risk

In Europe, most long-term care facilities (LTCFs) are for the elderly, including general nursing homes, residential homes and mixed facilities. According to a point prevalence survey on LCTFs and the Health care-Associated Infections in LCTFs carried out in 2013 by the European Centre for Diseases Prevention and Control (ECDC), there were approximately 63 224 LTCFs for older adults in EU/EEA Member States with a capacity of approximately 3.6 million beds(30). The size of Europe's LTCF population is increasing. Long-term care facilities are a heterogeneous group of organizations that provide care to a broad spectrum of persons. Patients range from paediatric to geriatric and may be admitted for psychiatric as well as medical care. Institutionalization for the patient may be permanent or for a period of rehabilitation with a view to subsequent discharge to the community or to another facility. The majority of LCTFs, however, provide care for elderly persons who reside permanently in these facilities. Health care associated infections are common among residents in LCTFs, with a frequency comparable to rates observed in acute care facilities. Because of age-related dysfunctions of the immune system and physiological changes, the elderly are more sensitive to infection and therefore predisposed to the most frequent infections occurring in nursing homes: urinary tract infections, pneumonia, skin and soft tissue infections and gastro-intestinal infections, in particular those for which previous antibiotic use is a risk factor, such as Clostridium difficile infection. Outbreaks are not uncommon, with influenza A virus and gastrointestinal infections the most frequent and severe.

Persons residing in LTCFs thus present a population which is very susceptible to the acquisition and spread of infectious diseases and for whom the consequences of infection may be very serious. The presence of multiple co-morbidities, frailty, senescence of the immune system and nutritional deficiencies may all contribute to more severe disease and the increased risk of death, with nursing home residents being at the greatest risk due to their close living quarters, shared caregivers, and opportunities for introduction of health care associated infections and the spread of pathogens to other facilities through resident transfers and the movement of staff and visitors in and out of the home (31, 32).

The elderly make up the majority of the population requiring care at LTCFs and this group has also been shown to be at risk of severe influenza. A systematic review evaluating populations at risk for severe influenza related illness found that for seasonal influenza there was a statistically significantly

raised risk of hospitalization (odds ratio (OR) 4.65, 95% confidence intervals (CI) 1.74 to 12.41) and risk of death (OR 2.95, 95% CI 1.53 to 5.70) among elderly people (>65 years) compared with non-elderly people (33). Based largely on the presence of co-morbid conditions, the presence of 'any risk factor' was also found to be significantly associated with increased risk of pneumonia, hospitalization and mortality, although the quality and quantity of the evidence of the effect of different risk factors in the development of complicated and severe influenza was limited and rated as 'low' or 'very low' on GRADE assessment by the authors.

With the population in Europe aged 85 years and above projected to rise from 14 million currently to 19 million by 2020 and to 40 million by 2050, and the expectation that more than 30% of people will be aged over 60 years in many European countries by 2050, the proportion of the population in countries at all levels of development which requires long-term care is set to increase dramatically over the coming decades(34).

The burden of disease

Outbreaks of influenza caused by both influenza A viruses and influenza B viruses are well-documented in LTCFs but as morbidity and mortality vary from year to year, and between different communities and LTCFs, it is challenging to accurately estimate the actual burden of influenza in these institutions. A review of 206 reported infectious outbreaks in elderly care facilities across 19 countries between 1966 and 2008 identified 37 different pathogens, but influenza viruses caused the largest number of outbreaks (23%)(35). In the 49 outbreaks caused by influenza, the median attack rate in residents was 33% (range 4 to 94%), and among staff the median attack rate was 23% (range 3-58%). The median case fatality rate for residents was 6.5% (range 0 to 55%), with one staff member death in one of the reported outbreaks. Over three consecutive 9-year time periods between 1980 and 2008, there was no observed decrease in attack rates or case fatality rates. Greater exposure of health care workers (HCWs) to outbreak pathogens in LTCFs compared with those working in acute-care settings, increased physical contact between staff and residents, inadequacy of infection control programmes in LTCFs, lack of health care worker education and training about infection control measures and suboptimal staff vaccination coverage may explain the high-attack rates in staff (7). Infection in HCWs affects not only themselves and their immediate family but may further inhibit efforts to control an outbreak if staff shortages result in remaining staff having to care for both affected and unaffected residents (36).

Furthermore, in addition to the morbidity and mortality directly associated with influenza infection in LTCFs and in the context of the current climate of the threat of the spread of antibiotic-resistant

bacteria, more than 5% of the antibiotics prescribed to nursing home residents have been attributed to infection with influenza (37).

Influenza causes almost one quarter of outbreaks in long-term care facilities.

When an outbreak occurs, on average one third of residents will be affected.

Of the residents affected, on average 6.5% of the infections will be fatal.

Epidemiology

Outbreaks of influenza (and other respiratory virus pathogens) in nursing homes in the Northern hemisphere occur most commonly during the winter but may occur at any time of year, particularly in the autumn months before seasonal vaccination campaigns have been fully implemented, and in the spring when antibody titres may have declined in those who have been vaccinated(38, 39).

A diagnosis of possible influenza should therefore be considered throughout the year in order to facilitate rapid detection and prompt management.

Although summer outbreaks in the Northern hemisphere are quite rare, if the clinical presentation of illness is compatible with influenza, this possibility cannot be discounted because it is 'the wrong time of year'.

Incubation period and serial interval

The incubation period (time between infection and onset of symptoms) of influenza is typically short, usually reported as ranging from 1 to 4 days, although this range is not supported by high-quality evidence, being based largely on expert opinions and observational studies (40). A subsequent systematic review of 6 experimental studies of influenza A (85 observations) and 2 experimental studies of influenza B (78 observations), estimated the median incubation time as 1.4 days (95% CI 1.3-1.5 days) and 0.6 days (95% CI 0.5 to 0.6 days) respectively, with 95% developing symptoms by 2.8 days (95% CI 2.5 to 3.2) and 1.1 days (95% CI 0.9 to 1.3) respectively, although published data were limited and estimates may be affected by variation in definition of symptom onset, the use of healthy volunteers rather than high-risk individuals in experimental studies, route of transmission, and varying infectious dose(41).

A systematic review of the serial intervals (duration between symptom onset of a secondary case and that of its primary case) has recently been conducted for various respiratory infections (42). For influenza A(H3N2), reported values for the mean serial interval were from 3.1 to 3.5 days (4 studies), although from one further dataset giving dates of symptom onset the authors calculated a mean

serial interval one day shorter than this at 2.2 days (95% CI 2.1 to 2.4 days). Reported mean serial intervals for influenza B ranged from 3.4 to 4.9 days (2 studies).

A relatively short incubation period and serial interval between cases enables the virus to spread rapidly through communities. Mitigation measures such as isolation and standard and transmission-based precautions should be instigated as soon as a case of suspected influenza is identified in order to minimise the risk of transmission to contacts.

Viral Shedding

Viral shedding is generally considered to be a proxy for influenza infectiousness (43-45). Volunteer challenge studies involving generally healthy adults have shown a rapid increase in viral shedding during the first day after inoculation, peaking on day 2, with an average duration of shedding of 4.8 days (95% CI 4.31-5.29) and with most healthy volunteers having cleared virus by days 6-7 (40). Viral shedding preceded clinical illness by one day in these studies. Household studies of natural influenza infection, which are thus more generalizable to community settings, have also shown pre-symptomatic shedding in up to one-third of cases. Clinical symptom scores followed a comparable course to viral shedding dynamics, with peak shedding for seasonal influenza A virus infection at 1-3 days after symptom onset (46-49). It is likely to be reasonable to assume that clinical illness profiles (presence of symptoms) may be used as a proxy for clinical infectiousness for seasonal influenza A infection. Some studies suggest that patterns of viral shedding for influenza B infections may be more variable with a bimodal peak and prolonged shedding for 6 to 7 days after symptom onset (47, 49).

Prolonged viral shedding has, however, been reported in children (48, 50, 51), in patients hospitalised with severe influenza (52), and in immunocompromised patients (53), in whom prolonged shedding may last weeks or even months (54, 55). To our knowledge there are no studies that have examined the transmission dynamics of influenza infections specifically in nursing home residents, the majority of whom are likely to be aged over 65 and many of whom will also have co-morbidities. In a prospective observational study of 147 hospitalised influenza patients, age greater than 65 and the presence of major co-morbidities were variables which were significantly associated with prolonged shedding of virus and higher viral load (52). Although there is bias in this study reflecting the severity of illness in these patients which caused them to be admitted, the possibility of continued shedding of patients discharged from hospital back to a LTCF having had a diagnosis of influenza should be considered as a possibility and appropriate infection control measures implemented.

LTCF residents discharged back to a LTCF from hospital after having had influenza should undergo a risk assessment with regard to the need for continued isolation and application of transmission-based precautions.

Asymptomatic viral shedding

There are limited data on the infectivity of people who shed virus but are asymptomatic or have subclinical infection. A pooled mean asymptomatic fraction of influenza infections of 16% (95% CI 13% to 19%) has been estimated in a recent systematic review of studies from outbreak investigations, but with considerable variation between studies that used virologic methods to confirm the presence of influenza compared with serologic testing, and also as a result of the inclusion of some cases of mild infection(56). Whilst some studies have reported no substantial difference in the amount of shedding between asymptomatic and symptomatic patients(46), others have found that viral loads in asymptomatic people are lower and shedding is of shorter duration, suggesting that they may be less efficient transmitters of disease(40, 48, 57). A systematic review examining the relationship between asymptomatic or pre-symptomatic shedding also found negligible, if any, evidence that such individuals have an important role in transmission (58).

Modes of transmission

Understanding how influenza is transmitted, together with the duration of infectiousness of those infected, are critical factors informing which control measures are likely to be effective in outbreak situations.

Influenza virus replicates in the epithelium of the upper and lower respiratory tract, entering and exiting the body via the mouth and nose. Infected hosts may release virus into the environment during breathing, talking, coughing and sneezing, producing a spray of virus-containing particles which are a continuum of different sizes ranging from 0.01µm to 500µm (59). Three routes of transmission are recognized:

- Droplet – larger sized particles >10µm which can land on the mucosal surfaces of the upper respiratory tract but are too large to be inhaled into the lungs and settle quickly to the ground or other surface, usually within 1-2 metres of the source of generation.
- Aerosol (droplet nuclei) – small particles less than 5µm which can remain suspended in the air much longer than droplets and are potentially inhalable into the lower respiratory tract and may produce more severe illnesses (based on data from experimental studies)(60).

- Contact – transfer of infectious particles to the mucous membranes via direct contact or indirect contact through touching contaminated objects (fomites).

Additional research is required to fully elucidate the epidemiology of transmission of specific ARIs from patients to health-care workers, and to other patients, during care delivery in health-care settings: with and without the use of specific precautions; with the use of triage and early identification alone versus its use in combination of other selected precautions; and with the use of spatial separation alone versus spatial separation with the use of other selected precautions. In relation to spatial separation, high-quality epidemiological studies are needed to examine the effect of discrete parameters (e.g. 1 m, 2 m) of spatial separation on the reduction of transmission and infection by ARIs.

Droplet and aerosol transmission

The relative importance of each of these routes in influenza transmission is unclear and the contribution of aerosolised infectious droplet nuclei has been particularly contentious. Droplets with a diameter of >8μm constitute >99% of the volume of expiratory spray during coughing, so although natural coughing may produce large numbers of smaller particles, their relative volume is low and the majority of virus particles will be contained in larger droplets which do not disperse widely and for which close proximity to the infectious source would be required for transmission Although there have been many studies that have demonstrated that influenza viruses can survive in artificially generated airborne aerosols for varying amounts of time, the relevance of such studies to natural routes of infection has been called into question (18). Viable influenza virus has been detected in exhaled breath and forced cough samples of naturally infected hosts, albeit at low levels, which adds evidence to support the potential for aerosol transmission (61-64). Disease transmission via aerosols is likely to be affected by host factors such as type and frequency of respiratory activity, site of infection, and viral load, together with extraneous factors such as relative humidity, evaporation and particle aggregation (59), but direct evidence that naturally produced aerosolised particles are able to survive the journey into a susceptible host and to spread disease is still lacking (65). Further transmission studies are required in this area.

An aerosol-generating procedure is defined as any medical procedure that can induce the production of aerosols of various sizes, including droplet nuclei. There is a significant research gap regarding the epidemiology of ARI transmission from patients to health-care workers during aerosol-generating procedures, particularly with respect to pathogens other than SARS-CoV. This gap is compounded by a lack of precision in the literature with regard to the definition for aerosol-

generating procedures. In addition, little information exists on the minimum ventilation requirements to reduce pathogen transmission during such procedures. There is no evidence to suggest a difference in the effectiveness of particulate respirators over medical masks as a component of PPE for routine care; however, research is needed to determine whether there is a difference between the effectiveness of particulate respirators and medical masks in the context of aerosol-generating procedures that have been consistently associated with increased risk of pathogen transmission.

Some medical interventions carry the risk of generating aerosols as they are carried out, which has implications for the recommendations for personal protection and infection control measures. A systematic review of 10 non-randomized studies which evaluated the risk of transmission of acute respiratory infections to health care workers caring for patients undergoing aerosol-generating procedures (AGPs) compared with HCWs not exposed to patients undergoing AGPs, found a significantly increased risk of transmission of severe acute respiratory syndrome (SARS) with endotracheal intubation (8 studies), non-invasive ventilation (2 studies), tracheostomy (1 study) and manual ventilation before intubation (1 study)(16). No significant difference between the groups was found for any of the other procedures evaluated (suction, manual ventilation after intubation, bronchoscopy, nebuliser treatment, manipulation of oxygen mask or bi-level positive airway pressure (BiPAP) mask, defibrillation, chest compressions, nasogastric tube insertion, high-frequency oscillatory ventilation, collection of sputum, high-flow oxygen, endotracheal aspiration, suction of body fluid, oxygen administration, chest physiotherapy and mechanical ventilation). Using the GRADE criteria all the studies were classified as very low quality and there is a research gap here regarding the risk of transmission of pathogens and the type of procedure. In the context of LTCFs, it should be taken into account that some residents with disabilities may require some high-risk AGPs.

Contact transmission

In addition to transmission by large droplets, some common respiratory pathogens (e.g. parainfluenza and respiratory syncytial virus) can be transmitted through contact – particularly by hand contamination and self-inoculation into conjunctival or nasal mucosa. Contact transmission may also play a role in avian influenza A(H5N1) and SARS infections. Infectious particles may either be transferred from an infected host to the mucous membranes of a susceptible individual directly and without involvement of a contaminated surface (direct transmission), or indirectly via a combination of hands or other body part and contaminated inanimate surfaces or objects (indirect transmission). The role of indirect transmission in particular, relative to other routes of transmission is debateable. The presence of influenza virus on hands and inanimate surfaces has been shown in

several studies (15), but with much heterogeneity in terms of swab positivity and survival times, ranging from a few hours to several days. This is likely due to methodological differences between studies and variability in the strains used, detection methods, viral titre inoculated, surface substrate, temperature and relative humidity. Few studies however have demonstrated the presence of viable virus potentially capable of transmitting infection on the hands or in the near environment of naturally infected people. Even when viable virus is present, it appears only in a relatively small proportion of samples and at low levels, which may indicate that an infectious dose may not persist along the transmission chain of indirect contact for this route to be significant in influenza (19, 66, 67). Nevertheless, there is some support for the concept of 'super-spreaders' for whom higher nasal viral loads and higher symptom scores are significantly associated with positive surface swabs , and it is possible that these individuals may have a role to play in spreading infection via the indirect contact route (19).

Uncertainties remain regarding the relative contributions to the spread of influenza by the different routes, but it is likely that each may have a role that will depend upon the circumstances at the time. Each of the three routes should therefore be separately addressed by infection control and prevention policies.

Health care workers as vectors of infection

Transmission of influenza from HCWs to hospital patients, including those in geriatric facilities, has been well documented using epidemiological linkage and nucleotide sequence analysis (68-70). Recently, wearable proximity sensors have been used to map and quantify face-to-face contacts (within a range of 1 to 1.5m) between HCWs, their patients and other HCWs, as a novel tool for the measurement of contact patterns in hospitals. These can highlight important aspects that impact upon the spread of infectious diseases (71, 72). Much heterogeneity appears to exist both for contact numbers and duration of contact across individual HCWS, although contact patterns from day to day of the study period appear consistent (72). Furthermore, only a small proportion of HCWs accounted for 42% of all the contacts including at least one patient, suggesting a population of individuals who could act as 'super-spreaders' of pathogens transmitted in the near environment of the patient. By combining such contact data with virological data, it has been demonstrated that infectious doctors and nurses were likely sources of hospital-acquired influenza for patients within a geriatric unit, and similarly that infectious patients were sources of infection for HCWs (73).

A systematic review and meta-analysis of 29 studies (14 randomized controlled trials and 15 prospective cohort studies) which attempted to compare the incidence of influenza in HCWs

compared with other workers not working in a health care setting, taking in account the vaccination status, found estimated incidence rates (IRs) for all influenza (symptomatic and asymptomatic) for unvaccinated HCWs was 18.7/100 population/season (95% CI 15.8 to 22.1) and for vaccinated HCWs was 6.5/100population/season (95% CI 4.6 to 9.0), both higher than the IRs in unvaccinated and vaccinated other workers (5.4/100 population/season (95% CI 3.0 to 9.8) and 1.2 (95% CI 0.9 to 1.7) respectively)(74). The authors did not however find a statistically significant difference between symptomatic infection incidence rates in HCWs compared to other workers, suggesting the possibility that HCWs may be at higher risk of asymptomatic or subclinical infection, and may thus act as an infective pool to transmit influenza to frail elderly people. The main limitation of the review is that data were obtained from different arms of the various eligible studies so pooled incidence rates may not be directly comparable between groups. A serological study of 518 HCWs in an acute hospital (accommodating patients with an average length of stay of 18 days or less), during a mild epidemic season, found that 23% of them had serological evidence of influenza infection, implying a potential transmission risk to patients given that between 28% and 59% of infected workers had subclinical infections and continued to work (75). Although the role of asymptomatic people and those with only mild symptoms in spreading influenza is uncertain, it is of concern that HCWs often continue to work despite having symptoms and may act as a source of infection to those in their care (76, 77). Nursing home aides in particular have been shown in one Swedish study to be the occupational group at significantly greatest risk of continuing to work despite the feeling that, in the light of their perceived state of health, they should have taken sick leave (78).

If an outbreak of influenza is suspected a risk assessment with regard to the need for application of transmission-based precautions should be conducted.

Carers should be absented from work if they develop symptoms suggestive of influenza, because they might propagate or prolong an outbreak if allowed to work.

Evaluation of the evidence of the effectiveness of interventions

Vaccination of elderly people living in LTCFs

A WHO position paper on vaccines against influenza was published in 2012 and reference is made to this document (http://www.who.int/wer/2012/wer8747.pdf)(79).

A Cochrane systematic review conducted by Jefferson et al in 2009, an update on a previous review by the same authors, aimed to assess the effectiveness of influenza vaccine in preventing influenza, influenza-like illness, pneumonia, hospitalizations and mortality in people 65 years or over, with

separate analyses for those living in nursing homes and community dwelling older people (80). Thirty cohort studies provided data for LTCFs. The results of their meta-analyses are summarized in Annex C1. For elderly people living in closed communities the results suggest that vaccination may be slightly to moderately more effective than no vaccination at preventing influenza-like illness (24%), pneumonia (47%), hospitalization (49%), overall mortality (60%) and mortality from influenza or pneumonia (54%), although no significant protective effect against proven influenza was found. However, the evidence base for all these outcomes is very weak due to the observational nature of the included studies and the presence of bias in such studies, and the authors concluded that the poor quality evidence did not provide sufficient information on which to base guidance on the safety, efficacy or effectiveness of influenza vaccines in the elderly.

A later systematic review conducted by Chan et al (81) which included 11 observational studies in institutionalised older adults ≥60 years also found that vaccination may have a small significant protective effect against pneumonia (37%) and mortality from influenza and pneumonia (34%), and they showed a trend towards protection against influenza like illness (21%), although this did not quite reach statistical significance (see Annex C1). The authors did not address the effectiveness of vaccination against all-cause mortality and due to an insufficient number of studies were unable to perform meta-analyses for laboratory-confirmed influenza or hospitalization. Only studies that accounted for differences in co-morbidities and/or functional status between the vaccinated group and the control group were eligible for inclusion in this systematic review in an attempt to minimise frailty bias. Although the results of their meta-analyses were comparable with the systematic review by Jefferson (80), again the quality of the evidence is very weak and does not definitively answer the uncertainty regarding the effectiveness of influenza vaccination in older people living in LTCFs.

Selection bias in which people who are particularly frail or close to death may not receive vaccine resulting in overestimation of the effectiveness of vaccine on mortality may be a particular problem (healthy recipient effect)(82, 83). Observational studies to examine vaccine effectiveness are methodologically challenging, but it is unlikely that an adequately powered placebo controlled randomized controlled trial (RCT) would be approved on ethical grounds to answer the uncertainties in this vulnerable population. As it is currently not possible to draw definitive conclusions from the current evidence base on the effectiveness of seasonal vaccinations in the elderly nursing home population, annual vaccination of residents as recommended in the majority of countries should still be encouraged.

WHO recommends annual influenza vaccination of residents prior to the influenza season unless contra-indicated.

Vaccination of HCWs to protect patients

An updated Cochrane systematic review by Thomas et al (84) evaluated the effectiveness of vaccinating HCWs working in institutions caring for the elderly in the prevention of proven influenza, lower respiratory tract infection, and hospitalization or death due to lower respiratory tract infection in elderly people over 60 years living in LTCFs. Outcome data from three cluster RCTs (5,896 participants) were analysed. The results (summarized in Annex C2) indicated no significant protective effect of vaccinating HCWs against these outcomes for elderly people regardless of the elderly patients' vaccination status. However, the effect estimates were imprecise and all the included studies were at high-risk of bias, so the quality of the evidence is very low. Two studies (a cluster RCT (85) and a cohort study (86)) which had been included in the previous version of this review (87) were excluded from the most recent update as the main outcomes were influenza-like illness and all-cause mortality; both non-specific outcomes which the authors felt the vaccines were not designed to address. In conclusion, the authors considered there was no evidence to make HCW vaccination mandatory.

A recent systematic review by Ahmed et al (88) which did include influenza-like illness (ILI), all-cause hospitalization and all-cause mortality as outcomes in patients in health care facilities, found a significant reduction in ILI and all-cause mortality associated with vaccination of HCWs (42% and 29% reductions respectively), but no significant reductions for laboratory-confirmed influenza or all-cause hospitalizations. These results were obtained from 4 cluster-RCTs presenting data on 116 LTCFs and are summarized in Annex C2. Four observational studies were also included in the review and synthesised narratively, which indicated that HCW vaccination was associated with a lower risk of ILI. Quality of evidence (GRADE) evaluations by the authors rated the evidence as low or very low quality, with the exception of the RCT mortality outcome which was moderate, and the conclusion was made that HCW influenza vaccination can enhance patient safety. As pointed out by Michiels, the suggestion of a protective effect of HCW vaccination against non-specific outcomes may be an indication of unaccounted cluster biases in the studies in this review, such as differences in hand-washing or other infection control precautions taken by care givers in the institutions which were randomized (89).

Narrative synthesis of data from the RCTs included in the earlier version of the systematic review by Thomas et al 2010 (87), combined with data from additional observational studies suggested a uniform direction of effect across multiple outcome measure, suggesting that HCW vaccination may offer some protection to vulnerable people and adds support to the current recommendations for vaccinating HCWs(90). The results are summarized in Annex C2.

There is a limited amount of evidence that influenza vaccination is protective against laboratory-confirmed influenza in the HCWs themselves. Inactivated trivalent vaccines have been found to have a protective effect against proven influenza in healthy adults (overall protective effect in vaccine matched and vaccine poorly-matched seasons 62% (95% CI 56% to 67%)(91). However, a systematic review which specifically addressed the effectiveness of seasonal influenza vaccination in HCWs found only 3 RCT matching the inclusion criteria, and only one of these(92) reported serologically-confirmed infections in 359 participants, with a vaccine effectiveness estimate of 88% (95% CI 59% to 96%, p=0.0005)(93).

Poor vaccine uptake by HCWs has been well-documented. In Europe, coverage of HCWs (including those working in LTCFs) varies between countries and is generally much lower than for other vaccination targeted groups, ranging from 9.5% to 75% with a median vaccination coverage rate of 28.6% (94). Reasons given for declining vaccination include fear that the vaccine will cause influenza, fear of side effects, dislike of injections, lack of awareness of the availability of the vaccine, forgetting or lack of time, and perceived low risk of contracting influenza (95). Targeting these areas of concern through staff education programmes and provision of information about vaccination may help to improve vaccination coverage, and allow a more conclusive evaluation of the effect of very high levels of LTCF staff influenza vaccination on outcomes in the residents in their care.

HCWs are at increased risk of contracting influenza at work and further transmitting infection to colleagues and residents.

Vaccination will provide protection to the HCW themselves and act as a barrier against spread of infection.

An uninfected workforce helps to maintain care delivery in outbreak situations.

Annual vaccination should be offered to all LTCF staff.

LTCF staff should be encouraged to be vaccinated.

HCWs should receive up-to-date information about the potential benefits of vaccination that specifically addresses reasons why vaccination might be declined, and should also receive education regarding the myths against vaccination.

Pneumococcal Vaccination

Secondary bacterial pneumonia, predominantly caused by *Streptococcus pneumoniae,* is a recognized complication of influenza, and has been estimated to be responsible for up to 50% of seasonal influenza deaths in the United States (96). Pneumococcal infection secondary to influenza is

associated with a particularly poor outcome in the elderly and is a major cause of death (96). Polyvalent polysaccharide vaccines (PPV), and specifically the 23-valent PPV are recommended for use in the elderly by countries in the EU Member States that have recommendations on pneumococcal vaccination, rather than capsular vaccines. A systematic review and meta-analysis of 18 RCTs and 7 observational studies has attempted to evaluate the efficacy and effectiveness of pneumococcal polysaccharide vaccines (PPV)(97). Results are summarized in Annex C3. A strong protective effect against invasive pneumococcal disease (IPD) was found from meta-analysis of RCTs (OR 0.26 (95% CI 0.14 to 0.45), I^2 0%, p<0.00001) and from case-control and cohort studies (OR 0.48 (95% CI 0.37 to 0.61), I^2 31%). There was also of a strong protective effect against clinically and radiologically confirmed pneumococcal pneumonia (OR 26% (95% CI 0.15 to 0.46), I^2 0%, 10 RCTs, n=35483). Overall, it was unclear if vaccination decreases all-cause pneumonia in immunocompetent adults due to the degree of statistical heterogeneity between studies (I^2 85%), indicating that the overall estimate of effectiveness is not applicable to all population groups who have different risks and susceptibility to disease. On subgroup analysis there was evidence of efficacy against all-cause pneumonia in low-income countries (OR 0.54, (95% CI 0.43 to 0.67), I^2 19%), but this was not significant in high-income countries in either the general population (OR 0.71, 95% CI 0.45 to 1.12, I^2 93%) or in adults with chronic illness (OR 0.93, 95% CI 0.73 to 1.19, I^2 10%). Vaccination with PPV was not associated with substantial reductions in all-cause mortality (OR 0.90, 95% CI 0.74 to 1.09, I^2 69%) compared with no vaccine. Although the vaccine appeared less efficacious in adults with chronic disease, this needs to be interpreted with caution and may be due to under-powering of the RCTs analysed due to under-recruitment of participants with underlying diseases. Furthermore, the results from this systematic review may not be generalizable to people living in LTCFs, who are often excluded from participating in RCTs and therefore not well-represented in studies of this design. This is exemplified in the recent CAPITA trial to evaluate the efficacy of the 13-valent pneumococcal polysaccharide capsular conjugate vaccine (PCV13) against pneumococcal community-acquired pneumonia in 84,496 adults 65 years or older (98). Among older adults, the PCV13 vaccine was efficacious in preventing vaccine type pneumococcal pneumonia and IPD (efficacy 46% (95% CI 22% to 62%) and 75% (95% CI 41% to 76%) respectively), although not significantly efficacious in preventing all-cause pneumonia (5.1% (95% CI -5% to 14%). However, nursing home residents were specifically excluded from participating in this trial.

Data from observational studies have, however, suggested that dual seasonal influenza and pneumococcal vaccination may have an additive effect resulting in greater reductions in hospitalization for pneumonia and deaths in the elderly than either of the vaccines alone. A cohort

study of 1898 elderly people with chronic lung disease and living in a care home found that concomitant vaccination against influenza and pneumococcal disease was more effective against hospitalization for pneumonia (63%, 95% CI 29% to 80%) and death (81%, 95% CI 68% to 88%) compared with no vaccine and more effective than for either vaccine alone (99). A similar additive effect was found in a study of 124,000 people aged 65 years and older in Sweden (100). Both influenza vaccine and PPV23 given alone showed a reduced, although non-significant, risk of hospital admission for influenza and pneumonia respectively, but the risk was significantly reduced in the group that received both vaccines compared with those who were unvaccinated (37%, 95% CI 19% to 50%). A cohort study of 532 nursing home residents during the 2009 influenza pandemic also found that dual vaccination significantly reduced all-cause mortality and mortality from pneumonia (hazard ratio (HR) 0.54, 955 CI 0.35 to 0.84) and 0.60, 95% CI 0.35 to 0.99 respectively) compared with seasonal vaccination alone when there was a vaccine mismatch, and suggested that pneumococcal vaccination may be particularly important as a second line to decrease mortality when there is a mismatch between the prevalent influenza vaccine strain or during the emergence of a novel pandemic influenza strain (101).

A one-time pneumococcal vaccine in addition to annual seasonal influenza vaccine may reduce the risk of influenza-related complications in older people.

Non-pharmaceutical control measures

The effectiveness of non-pharmaceutical interventions (NPI) (hand hygiene, PPE use and social distancing) to control influenza outbreaks in LTCFs has been less thoroughly evaluated than has the effectiveness of vaccination and the use of antivirals.

Non-pharmaceutical interventions against influenza in the LTCF setting

Just one systematic review has examined the effectiveness of NPIs in the setting of the LTCF and specifically in the context of influenza. Rainwater-Lovett et al (12) (search date September 2011) sought reports of influenza outbreaks in LTCFs, finding 37 reports of 60 outbreaks meeting their inclusion criteria. The findings are summarized in Annex C4. The use of Personal Protective Equipment (PPE)(considered as glove and mask use, hand hygiene, and droplet precautions) appeared to be consistent with a protective effect but did not reach statistical significance (OR 0.63 (95% CI 0.33 to 1.19) for influenza A or B outbreaks in which PPE was used compared with attack rates in outbreaks where infection control measures were not implemented and adjusting for use of antivirals. Social distancing was not observed to have any significant effect. However, all the included studies were reports of outbreaks and subject to considerable outcome reporting bias, with

the focus being particularly on pharmaceutical interventions and likely underreporting of NPI. Furthermore, definitions of NPI when used were broad and rarely reported in detail, so the quality of the evidence is poor.

Physical interventions

Other systematic reviews have addressed the effectiveness of NPIs although not necessarily restricted to the transmission of influenza, nor in the LTCF setting. A large Cochrane systematic review by Jefferson et al (2010)(10), an update of an earlier version(102), examined the effectiveness of physical barriers, including the use of hand hygiene, PPE, and social distancing (defined in the review as spatial separation of at least one metre between those infected and non-infected), in reducing the spread of respiratory viruses. Sixty-seven studies of various designs (RCTs, cluster-RCTs and observational studies) were included in the review. Evidence from the best-quality cluster-RCTs suggested that hand-washing can prevent transmission, particularly when aimed at young children or households with young children although the studies from which this evidence came were also at high risk of confounding. Meta-analysis of the case-control studies, which were considered sufficiently homogeneous to allow pooling, indicated that barriers to transmission, isolation and hygiene precautions were significantly effective at reducing the transmission of respiratory viruses (results summarized in Annex C5). Medical masks (either surgical masks or N95 respirators) appeared to perform most consistently, with no evidence that respirators were superior to simple masks in decreasing transmission. However, most of the review related to SARS rather than influenza and all settings were included so the review's findings may not be generalizable to the transmission of influenza in LTCFs (10).

The effectiveness of control measures to prevent transmission of respiratory syncytial virus (RSV) has been addressed in a systematic review which included 21 relevant experimental and observational studies, all of which were conducted in a neonatal/paediatric setting or in units accommodating immunocompromised adults (103). Multicomponent strategies (e.g. cohort nursing, PPE, isolation) were found to be broadly successful in reducing nosocomial transmission, with PPE intervention using eye protection appearing to be more effective than those using gowns and masks. However, the authors noted the lack of high-quality evidence and highlighted the need for further research to identify the most effective and cost-effective individual control measures.

Masks and particulate respirators

Additional systematic reviews have focussed on specific infection control practices. The use of masks and particulate respirators to prevent transmission of influenza was considered by bin-Reza et al (13)

in a systematic review updated in January 2011 (summarized in Annex C4). Seventeen eligible studies were identified, of which 8 were RCTs, 8 were case-control studies, and 1 was a cohort study. Six of the 8 RCTs found no significant differences between control and intervention groups (masks with or without hand hygiene; N95/P2 respirators). One household RCT found decreased secondary transmission of upper respiratory tract infection/ILI/laboratory-confirmed influenza in those who wore masks coupled with alcohol-based hand sanitizer use compared with education alone (104), and a cluster RCT based in a hospital setting found lower rates of clinical respiratory illness associated with non-fit-tested N95 particulate respirators compare with medical masks. Of the 9 included observational studies, 8 found that mask and/or particulate respirator use was independently associated with reduced risk of SARS. Again the applicability of this to influenza has to be questioned, not least because the period of infectivity is known to be different for SARS-CoV and influenza, but also as compliance with protective measures may be affected by a difference in the perceived threat of the different diseases. Results from this systematic review suggest that the evidence base for the effectiveness of masks and/or particulate respirators is currently limited.

Cowling et al (14) had previously also found few data to support the use of masks or respirators to prevent becoming infected in an earlier systematic review and narrative synthesis (summarized in Annex C4). However, they did find limited evidence that wearing of masks or respirators by those infected with influenza may protect others, although this evidence is based on one experimental volunteer study which did not consider the potential for leakage around the edge of the mask, penetration of viruses through the mask, or the functioning of the mask under different conditions of temperature and humidity. Since then, a further experimental study has demonstrated that medical masks nearly eliminate viral RNA detection in the coarse aerosol fraction with a 25 fold (95% CI 3.5 to 180) reduction in the number of viral copies, and a statistically significant 2.8 fold (95% CI 1.5 to 5.2) reduction in viral copies in the fine aerosol fraction, and an overall 3.4 fold (95% CI 1.8 to 6.3) reduction in viral aerosol shedding (61). Although the evidence remains limited, there may be a role for the wearing of medical masks by patients (likely to be symptomatic shedders) if feasible and tolerable, particularly if they have to be taken out of their own room or isolation area.

Superiority of NIOSH-certified (N95) or equivalent particulate respirators over medical masks in protecting HCWs against acute respiratory infections has not been shown. Smith et al conducted a systematic review (105) of both clinical and surrogate exposure data (laboratory studies of filter penetration, face-seal leakage, and total inward leakage) comparing respirators with masks. Although laboratory tests suggested that particulate respirators had a protective advantage over medical masks, no significant difference in the risk of laboratory-confirmed respiratory infection or

ILI was noted in clinical settings (results summarized in Annex C4). However, there were insufficient data to make a definitive conclusion, the majority of the included studies did not audit compliance with either intervention, and potential confounders such as the use of other PPE and hand hygiene were not accounted for in the meta-analysis. An experimental study using a dummy head attached to a breathing simulator to test the performance of medical masks against an influenza challenge demonstrated that masks are to some extent protective against live aerosolised virus (106). On average a 6-fold reduction in live virus was noted in the air behind the mask compared with air in front (depending upon the design of the mask), although live virus was extracted from the air behind all the masks tested. Further research is required to establish whether medical masks confer adequate protection to the wearer against aerosols, and whether the protective effect is due to the mask itself or by minimising touching of oral and nasal mucosae.

Hand hygiene

Several systematic reviews have attempted to evaluate the effectiveness of hand hygiene measures on the risk of acquiring respiratory infection, although again not specifically influenza infection, nor in LTCF settings. Two meta-analyses estimated a reduction in community acquired respiratory infections of 16% (95% CI 11 to 21%) to 21% (95% CI 5% to 34%) by implementation of various interventions, including educational measures, use of antibacterial soap, non-antibacterial soap, alcohol based sanitizer, benzalkonium hand sanitizer and layered interventions (soap/sanitizer combined with education)(107, 108). Aiello et al (2008) (107) found that use of non-antibacterial or antibacterial soap with education, and benzalkonium chloride–based hand sanitizer were efficacious at reducing respiratory illness compared with controls (RR 0.49 (95% CI 0.40 to 0.61), 1 study for non-antibacterial soap; RR 0.50 (95% CI 0.40 to 0.61), 1 study for antibacterial soap; RR 0.60 (95% CI 0.45 to 0.81), 2 studies for benzalkonium chloride sanitizer), but the use of alcohol based sanitizers (with education) had no significant effect (RR 0.93 (95% CI 0.84 to 1.03), 6 studies). Studies included in these systematic reviews were generally of poor-quality, with methodological flaws and provided very limited data on compliance.

More recently, Wong et al (11) conducted a meta-analysis which included 10 RCTs evaluating the effect of hand hygiene interventions specifically against influenza infections in the community, although only in open settings without confinement and special care for the participants (therefore excluding LTCFs). They found that the combination of hand hygiene with medical masks had a statistically significant effect against laboratory confirmed influenza (RR 0.73 (95% CI 0.53 to 0.99), I^2 0%, p=0.05, 5 studies, n=4,050) whereas hand hygiene alone did not (RR 0.90 (95% CI 0.67 to 1.20), I^2 14%, p=0.47, 4 studies, n=6,035) (summarized in Annex C5). The GRADE quality of the evidence was

assessed as high. Although hand hygiene appeared to have no significant effect on either laboratory confirmed infection or ILI, the authors caution that this does not necessarily mean that hand hygiene itself is ineffective, but rather may raise questions about compliance with existing recommendation and failure to practice correct hand hygiene at critical contamination points.

Non-pharmaceutical interventions should be combined to target the different potential modes of transmission of influenza rather than focussing on a single individual intervention.

Compliance with NPIs is likely to affect their effectiveness and the importance of this should be emphasised to staff.

Antivirals

There has been much debate in recent years regarding the efficacy and effectiveness of antivirals in the prophylaxis and treatment of influenza. Although neuraminidase inhibitors are widely licensed and prescribed across Europe for the treatment of influenza, evaluation of their efficacy has been hampered until recently by the lack of accessibility of unpublished trial data, resulting in an incomplete evidence base. The incorporation of unpublished trial data and analysis of individual patient data into recent systematic reviews and meta-analyses has allowed for more complete assessment of the effects of the NAIs, although gaps and uncertainties remain in the evidence base, and there remains a paucity of evidence to fully inform the optimal approach to the management of influenza in LTCFs.

Treatment using neuraminidase inhibitors (NAIs)

Results from recent relevant systematic reviews of influenza treatment are summarized in Annex C6.

Time to alleviation of symptoms

There is evidence from meta-analyses of RCTs that NAIs can produce a significant, although modest, reduction in the time to first alleviation of symptoms in previously healthy adults (16.8 hours ($p<0.0001$) in the Cochrane systematic review by Jefferson et al(23), 17.8 hours ($p<0.0001$) in the intention-to-treat (ITT) population treated with oseltamivir in the systematic review by Dobson et al(109), and 13.3 hours ($p=0.008$) for oseltamivir and 13.7 hours for zanamivir ($p=0.02$) in that by Burch et al(110). Overall these reductions represented a 10% to 15% reduction in overall duration of symptoms for those treated with an NAI compared with those receiving placebo. Similar significant reductions were also found in meta-analyses of observational studies for both oseltamivir and zanamivir compared with no antiviral treatment, although the quality of the evidence was very low for oseltamivir and moderate for zanamivir (111). However, in elderly people this effect appears to

be attenuated, and no significant difference was found between those treated with an NAI and those receiving placebo.

Viral excretion as a marker of effect, the duration and quantity of which may contribute to the spread of infection, was unreliable in antiviral treatment trials due to fluctuating patterns and failure within trials to demonstrate a series of negative samples, and the authors asserted that the capacity of oseltamivir to interrupt viral transmission and decrease complication are not supported by any data they were able to access (23).

Hospitalization

In the general population hospitalization is a relatively uncommon event in seasonal influenza. For previously healthy adults, Jefferson et al (23) found no significant difference in hospitalization rates for oseltamivir treated adults compared with those receiving placebo, although it was noted that 'hospitalization' was a poorly defined outcome in the included trials and inconsistently reported. Similarly no significant effect was found in the previously healthy adult population by Burch et al (110), nor by Dobson et al (109) in the intention-to treat population treated with oseltamivir, although a significant reduction was seen in the influenza-confirmed intention-to-treat population (ITTI) (RR 0.37 (95% CI 0.17 to 0.81), p=0.013).

A meta-analysis of observational studies indicated a potential effect of oseltamivir in reducing hospitalization in the general population (all ages) compared with no antiviral (adjusted OR 0.75 (95% CI 0.66 to 0.89), p<0.0001, 4 studies, n=150,710), but no significant effect was found for inhaled zanamivir (OR 0.66 (0.37 to 1.18), I^2 0%, p=0.16 (2 studies, n=4,761) although confidence in the effect estimate was very low because of imprecise and possibly biased hospitalization data (111). Early oseltamivir treatment (within 48 hours of onset) reduced hospitalization compared with later treatment (unadjusted OR 0.52 (95% CI 0.33 to 0.81), I^2 0%, p=0.004 (2 studies, n=597), with a further included study showing a reduction in duration of hospitalization of 24 hours (95% CI 0 to 48 hours) with early treatment(111).

Data were limited for evaluation in elderly people; one study in the ITTI population found no significant difference in elderly individuals requiring hospitalization between oseltamivir treated people and those receiving placebo (OR 0.42 (95% CI 0.11 to 1.60) (1 study, n=477), but there were no studies found for zanamivir(110).

The low number of hospitalization events limits the power of these studies to detect potential effects so the results should be interpreted cautiously.

Pneumonia

Dobson et al (109) found reduced rates of lower respiratory tract complication in both the ITT and ITTI general adult populations (RR 0.56 (95% CI 0.42 to 0.75), p=<0.001, 9 studies, n=2,807; and RR 0.62 (95% CI 0.49 to 0.79), p=0.0001, 9 studies, n=4,202 respectively). However, the included studies reported data based on patient-reported pneumonia and there was no distinction in the trials between pneumonia caused by influenza and secondary bacterial pneumonia. Jefferson et al(23) also found an effect of oseltamivir on the overall relative risk of pneumonia (RR 0.55 (95% CI 0.33 to 0.90), I^2 0%, p=0.02, 8 studies, n=4,452), but on subgroup analysis of the 5 trials that used detailed diagnostic data collection forms or reported radiological confirmation of pneumonia (as opposed to non-specific events), the effect was no longer significant (RR 0.69 (95% CI 0.33 to 1.44, p=0.32, n=1136). Other meta-analyses also found no statistically significant difference between those adults treated with either oseltamivir or zanamivir and placebo or no antiviral treatment (111, 112). Again the number of events was low and most trials do not aim to assess the impact of treatment on the risk of pneumonia and as such are likely to be underpowered to detect a genuine effect. Overall there is a lack of good evidence that NAIs reduce the risk of lower respiratory tract complications, including pneumonia.

Mortality

Analysis of individual patient data from 29,234 patients of all ages hospitalised with 2009 H1N1 pandemic influenza (Post-pandemic Review of anti-Influenza Effectiveness (PRIDE) study)(22) indicated that for this group of patients NAI treatment at any time was associated with a significant reduction in mortality (adjusted OR 0.81 (95% CI 0.70 to 0.93), p=0.002, but that the benefit tended to be lost if NAIs were started more than 48 hours after the onset of symptoms (adjusted OR 1.20 (95% CI 0.93 to 1.54), p=0.15 for those in whom treatment started late compared to those in whom early treatment was initiated). A reduction in mortality risk for patients receiving oseltamivir compared to those not given antivirals was also noted by Hsu et al(111) in their meta-analysis of observational studies (adjusted OR 0.23 (95% CI 0.13 to 0.43, p<0.00001, 3 studies n=681). No association with inhaled zanamivir treatment was observed although there was only data from one very small observational study (n=87) (111).

Side effects of NAIs

Both systematic reviews by Jefferson et al (23) and Dobson et al (109) found that patients taking oseltamivir as treatment were at increased risk of nausea and vomiting compared with those on placebo, although the risks of diarrhoea and cardiac events were significantly reduced. For inhaled

zanamivir, there appeared to be no significant risk of reported adverse events, but a decreased risk of nausea and vomiting (23). No significant increase in the overall risk of psychiatric or neurological disorders was found (23, 109), although Jefferson et al (23) noted a dose-response effect reported in two trials.

Overall, there is a paucity of evidence on the effectiveness of NAIs used to treat influenza in elderly people and those living in LTCFs. Although there is reasonable evidence that time to alleviation of symptoms is modestly reduced in previously healthy people, this effect appears to be attenuated in the elderly.

Early treatment with oseltamivir (<48 hours after onset) may reduce mortality in patients hospitalised with influenza, so early presumptive treatment may be useful in people living in LTCFs who are more likely to be hospitalised due to underlying conditions.

The balance of risks and benefits should be taken into account by clinicians when considering treating those living in LTCFs.

Prophylaxis using neuraminidase inhibitors (NAIs)

Results from recent relevant systematic reviews of influenza prophylaxis are summarized in Annex C7.

Two recent systematic reviews have found evidence to support the use of NAIs for the prophylaxis of influenza in individuals and households. Jefferson et al (23) reported a significant reduction in the risk of developing symptomatic seasonal influenza based on study report data from RCTs for both individuals in the community and for households (RR 0.45 (95% CI 0.30 to 0.67), I^2 0%, p=0.00009 (3 study reports, n=2,479) and RR 0.20 (95% CI 0.09 to 0.44), I^2 n/a, p=0.00007 (1 trial, n=405) respectively. Similarly, zanamivir was also shown to be effective at reducing the risk of symptomatic influenza in individuals and households (RR 0.39 (95% CI 0.22 to 0.70), I^2 45%, p=0.0015 (4 trials, n=5,275) and RR 0.33 (955 CI 0.18 to 0.58), I^2 40%, p=0.00013 (5 trials, n=1,525) respectively). There was further support for the effect of both oseltamivir and zanamivir in reducing the risk of laboratory-confirmed influenza in the systematic review by Okoli et al (24) (oseltamivir: OR 0.11 (95% CI 0.06 to 0.20), I^2 59%, p<0.001, for individuals and OR 0.23 (95% CI 0.09 to 0.59), I^2 39%, p<0.002 for households; zanamivir: OR 0.23 (95% CI 0.16 to 0.35), I^2 0%, p<0.001 for individuals and OR 0.18 (95% CI 0.10 to 0.31), $I^2$0%, p<0.001 for households). This meta-analysis included data from both RCTs and observational studies of seasonal and pandemic influenza, and considered the effectiveness of pre and post exposure prophylaxis as a combined entity (on the basis that in a rapid containment situation it will not be known if individuals are receiving pre or post exposure

prophylaxis). However, the main outcome measure was community transmission of influenza which was defined by the authors as epidemiologically linked cases in settings other than hospitals, care homes and nursing homes.

There is less evidence of the effectiveness of NAI prophylaxis in the elderly. The elderly and frail are often deliberately excluded as participants in RCTs, which calls into question the generalizability of the findings from such studies to this section of the population, and there are few studies in LTCFs. The efficacy of seasonal prophylaxis with oseltamivir in the frail elderly living in residential care has been shown in one study (RR 0.08 (95% CI 0.01 to 0.63) 1 trial, n=548)(113) although there were no studies of post-exposure prophylaxis for this group. Other studies have seen a non-significant effect of post–exposure prophylaxis and seasonal prophylaxis with zanamivir (25, 114). Furthermore, there have been no studies that have addressed the effectiveness of antiviral prophylaxis in HCWs.

Analysis of the side effects when taking NAIs as prophylaxis has been conducted by Jefferson et al (23). With oseltamivir the risks of headache, nausea, and psychiatric events were significantly raised (RR 1.18 (95 CI 1.05 to 1.33); RR 1.96 (95% CI 1.20 to 3.20); RR 1.80 (95% CI 1.05 to 3.08) respectively). However, in 2 of the 4 studies included in the analysis, participants were taking prophylaxis for 6 weeks, and duration was not specified in a third. No significant increase in reported adverse events was noted from the trials of zanamivir prophylaxis.

There is a lack of evidence of the effectiveness of antivirals in the control of outbreaks of influenza in LTCFs. Nevertheless, there is good evidence from household studies that NAI prophylaxis is effective at reducing the risk of influenza in the generally healthy adult population.

Given the limited evidence available on the effectiveness of seasonal influenza vaccination in older people and the high attack and mortality rates in LTCFs, prophylaxis with antivirals should be considered if they can be given in an organised and timely way.

Annex C – Tables of evidence

In the tables in this annex, results in bold type are statistically significant (p≤0.05).

C1 Summary of systematic reviews of influenza vaccine effectiveness in elderly people in LTCFs

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size for ORs and RRs	Summary
Influenza-like illness					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	12,388 people ≥65 years in LTCFs Data from 26 cohort studies	Overall VE	**RR 0.76 (95% CI 0.66-0.88), I^2 60%, p= 0.00015**	**Small** **24% (95% CI 12% to 34%**	**Favours vaccine**
Chan et al 2014(81)	7,801 institutionalised adults aged ≥ 60 years Data from 10 observational studies (cohort and case control studies)	Overall VE	OR 0.79 (95% CI 0.61-1.03), I^2 50%, p = 0.086	Not significant 21% (95% CI -3% to 39%)	No significant protective effect

Influenza					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	1,941 people ≥65 years in LTCFs Data from 8 cohort studies	Overall VE	RR 0.65 (95% CI 0.32 - 1.29), I^2 57%, p =0.22	Not significant 35% (95% CI -29% to 68%)	No significant protective effect
Influenza clinically defined but without clear definition					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	24,238 people ≥65 years in LTCFs Data from 7 cohort studies	Overall VE	RR 0.52 (95% CI 0.27 – 1.02), ***I^2 93%,*** p=0.056	Comment: Very high I^2 so pooled result not	No significant protective effect BUT high level of heterogeneity between studies
Pneumonia					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	10,274 people ≥65 years in LTCFs Data from 17 cohort studies	Overall VE	**RR 0.53 (95% CI 0.43 – 0.66), I^2 0%, p <0.00001**	**Small** **47% (95% CI 34% to 57%)**	**Favours vaccine**

Chan et al 2014(81)	7,572 institutionalised adults aged ≥ 60 years Data from 9 observational studies (cohort and case control studies)	Overall VE	**OR 0.63 (95% CI 0.47 – 0.82), I^2 0%, p= 0.01**	**Small** **37% (95% CI 18% to 53%)**	**Favours vaccine**
Hospitalization for ILI or pneumonia					
Jefferson et al 2010 (update of 2005 Cochrane systematic review)	28,032 people ≥65 years in LTCFs Data from 12 cohort studies	Overall VE	**RR 0.51 (95% CI 0.32 – 0.81), I^2 55%, p=0.0043**	**Small** **49% (95% CI 19% to 68%)**	**Favours vaccine**
Mortality from flu or pneumonia					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	32,179 people ≥65 years in LTCFs Data from 27 cohort studies	Overall VE	**RR 0.46 (95% CI 0.33 – 0.63), I^2 11%, p<0.00001**	**Moderate** **54% (95% CI 37% to 67%**	**Favours vaccine**

Chan et al 2014(81)	6,040 institutionalised adults aged ≥ 60 years Data from 9 observational studies (cohort and case control studies)	Overall VE	**OR 0.66 (95% CI 0.47 – 0.90), I^2 0%, p=0.001**	**Small** **34% (95% CI 10% to 53%)**	**Favours vaccine**
Overall mortality					
Jefferson et al 2010(80) (update of 2005 Cochrane systematic review(115))	305 people ≥65 years in LTCFs Data from 1 cohort studies	Overall VE	**RR 0.40 (95% CI 0.21 – 0.77), I^2 not applicable, p=0.0061**	**Moderate** **60% (95% CI 23% to 79%)**	**Favours vaccine**

C2 Summary of systematic reviews of effectiveness of vaccinating HCWs at preventing influenza in elderly people

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size	Favours
Proven influenza					
Thomas et al 2016(84) Cochrane systematic review (update of 2013 review (116))	752 people ≥60 years in LTCFs. Meta-analysis of data from 2 cluster RCTs	Overall effect for vaccinated and unvaccinated patients combined Comment: In 1 RCT patients were unvaccinated and in the other patients were either vaccinated or unvaccinated	RD -0.00 (95% CI -.03 to 0.03), I^2 0%, p=0.87 Adjusted study effect estimate RD 0.00 (95% CI -0.03 to 0.03)	Not significant	No significant protective effect to patients of vaccinating HCWs
Ahmed et al 2014(88) Systematic review	752 elderly people living in LTCFs Meta-analysis of data from 2 cluster RCTs (same RCTs included in Thomas et al)	Overall effect	RR 0.8 (95% CI 0.3-2.1), I^2 0%, p=0.64	Not significant	No significant protective effect to patients of vaccinating HCWs Comment: Authors' quality of evidence (GRADE) – Very Low

Dolan et al 2013(90) Systematic review	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study) Narrative synthesis of evidence from 1 published meta-analysis and 5 observational studies	Overall effect	n/a	Pooled data from the meta-analysis (2 RCTs)(Thomas et al 2010) showed small non-significant effect. Direction of effect supported by 2 observational studies (paediatric hospital and oncology hospital) showing statistically significant protective effect, but high risk of bias and imprecision due to very small sample sizes.	Direction of effect supported.
Outbreaks of laboratory confirmed influenza					
Dolan et al 2013(90)	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study) Narrative of 1 observational study in a nursing home setting	Effect	n/a	No statistically significant difference. Vaccination coverage appeared higher in homes experiencing outbreaks. Analyses unadjusted and imprecise due to small numbers.	No difference

Lower respiratory tract infection					
Thomas et al 2016(84) Cochrane systematic review (update of 2013 review(116))	1,059 people ≥60 years in LTCFs. Meta-analysis of data from1 cluster RCTs (presenting data separately for vaccinated patients and unvaccinated patients)	Overall effect for vaccinated and unvaccinated patients combined	RD -0.02 (95% CI -0.04 to 0.01), I^2 0%, p=0.15 Adjusted effect estimate RD -0.02 (95% CI -0.06 to 0.03)	Not significant	No significant protective effect to patients of vaccinating HCWs
Influenza-like illness					
Ahmed et al 2014(88)	7031 elderly people living in LTCFs Meta-analysis of data from 3 cluster-RCTs	Overall effect	**RR 0.58 (95% CI 0.46 – 0.73), I^2 13%, p=<0.0001**	**Small** **42% (95% CI 27% to 54%)**	**Favours vaccination of HCWs** Comment: Authors' quality of evidence (GRADE) – Low

Dolan et al 2013(90) Systematic review	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study). Narrative synthesis of evidence from 1 published meta-analysis and 5 observational studies	Overall effect	n/a	Pooled data from Thomas et al 2010 (now superseded) suggest significantly protective effect when adjusted for clustering; supported by observational data in this review with 2/5 studies (1 in paed unit, 1 in oncology hospital) demonstrating statistically significant effect, although noted to be at higher risk of bias.	**Favours vaccination of HCWs**
Outbreaks/clusters of ILI					
Dolan et al 2013(90) Systematic review	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study). Narrative synthesis of evidence from 3 observational studies	Overall effect	n/a	Statistically significant protective effect in all 3 studies, but different ILI definitions used, estimates imprecise and high risk of bias.	**Favours vaccination of HCWs**

Hospitalization for respiratory illness					
Thomas et al 2016(84) Cochrane systematic review (update of 2013 review(87, 116))	3,400 people ≥60 years in LTCFs. 1 cluster RCT (presenting data combined for vaccinated and unvaccinated patients)	Overall effect for vaccinated and unvaccinated patients combined	RD 0.00 (95% CI -0.02 to 0.02) Adjusted effect estimate 0.00 (95% CI -0.02 to 0.03)	Not significant	No significant protective effect to patients of vaccinating HCWs
Hospitalization – all causes					
Ahmed et al 2014(88)	5,972 elderly people living in LTCFs Meta-analysis of data from 2 cluster RCTs	Overall effect	RR 0.91 (95% CI 0.69-1.19), I^2 26%, p=0.47	Not significant	No significant protective effect to patients of vaccinating HCWs Comment: Authors' quality of evidence (GRADE) – Low
Dolan et al 2013(90)	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1			Pooled estimate from 2 RCTs with 3 different measures of effect in Thomas et al 2010 meta-analysis (now superseded) showed no significant effect	No clear effect

	study). Narrative synthesis of evidence from 1 published meta-analysis				
Deaths due to respiratory illness					
Thomas et al 2016(84) Cochrane systematic review (update of 2013 review(116))	4,459 people ≥60 years in LTCFs. Meta-analysis of data from 2 cluster RCTs for both vaccinated and unvaccinated patients	Overall effect for vaccinated and unvaccinated patients combined	RD -0.02 (95% CI -0.06 to 0.02), ***I^2 81%,*** p=0.4 Adjusted effect estimate RD -0.01 (95% CI -0.05 to 0.03), I^2 49%, p=0.55 Updated 2016 review did not combined data from the 2 studies	Not significant	No significant protective effect to patients of vaccinating HCWs
Dolan et al 2013(90)	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study). Narrative synthesis data	Overall effect	n/a	Pooled estimate of deaths from pneumonia (1 RCT) and respiratory deaths (1 RCT) in Thomas et al 2010 (now superseded) showed small non-significant protective effect, plus small non-significant effect from individual studies for ILI mortality and laboratory-confirmed influenza	No significant effect

	from 1 published meta-analysis			mortality.	
All-cause mortality					
Ahmed et al 2014(88)	8,468 elderly people living in LTCFs Meta-analysis from 4 cluster RCTs	Overall effect	**RR 0.71 (95% CI 0.59 to 0.85), I^2 0%, p=0.0003**	**Small** **29% (95% CI 15% to 41%)**	**Favours vaccination of HCWs** Comment: Authors' quality of evidence (GRADE) – Moderate
Dolan et al 2013(90)	People at increased risk of respiratory disease (mostly in LTCFs but included renal dialysis facility (1 study), paediatric hospital (1 study) and an adult oncology hospital (1 study). Narrative synthesis data from 1 published meta-analysis		n/a	Thomas et al 2010 (now superseded) from 4 RCTs suggest statistically significant protective effect when adjusted for clustering, although effect inconsistent but uniform in direction.	Vaccination of HCWs

C3 Summary of systematic review of vaccines for preventing pneumococcal infection in adults

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size	Favours
Invasive pneumococcal disease					
Moberley et al (2013)(97) Systematic review and meta-analysis of 18 RCTs and 7 non-RCTs	Adults from low and high income countries with and without chronic disease Meta-analysis of data from 36,489 people from 11 RCTs comparing Polyvalent Pneumococcal Polysaccharide Vaccines (PPV) to placebo. Meta-analysis of data from case-control and cohort studies (number of participants unspecified) comparing PPV with no pneumococcal vaccination	Overall effect and subgroup analysis according to low/high income countries, and adults with chronic disease	**Overall (RCTs):** **OR 0.26 (95% CI 0.14 to 0.45), I^2 0%, p<0.00001 (11 RCTs, n=36,489)** **Subgroup analyses:** **Low-income countries** **OR 0.14 (95% CI 0.03 to 0.61), I^2 n/a, p=0.01 (1 RCT only, n=5373)** High-income countries with chronic illness OR 1.56 (95% CI 0.35 to 6.94), I^2 0%, p=0.56 (5 RCTs, n=3,230) **High-income countries** **OR 0.20 (95% CI 0.10 to 0.39), I^2 0%, p<0.00001 (5 RCTs, n=27,886)** **Overall (observational studies):** **OR 0.48 (95% CI 0.37 to 0.61), I^2 31%, p<0.00001 (7 studies)**	**High overall efficacy 74% (95% CI 55% to 86%**)	**Favours PPV** Author's comment: vaccine efficacy in subgroup of adults with chronic disease appears poor in comparison to otherwise healthy adults, but studies judged to be underpowered due to number of participants recruited

			Subgroup analyses: **Immunocompetent adults** **OR 0.41 (95% CI 0.32 to 0.52), I^2 18%, p<0.00001)** **Older immunocompetent adults** **OR 0.32 (95% CI 0.22 to 0.47), I^2 0%, p<0.00001**		

All-cause pneumonia					
Moberley et al (2013)(97) Systematic review and meta-analysis of 18 RCTs and 7 non-RCTs	Adults from low and high income countries with and without chronic disease Meta-analysis of data from 47,734 people from 16 RCTs comparing PPV to placebo.	Overall effect and subgroup analysis according to low/high income countries, and adults with chronic disease	**Overall (RCTs):** **OR 0.72 (95% CI 0.56 to 0.93), I^2 *85%*, p=0.01 (16 RCTs, n=47734)** **Subgroup analyses:** **Low-income countries** **OR 0.54 (95% CI 0.43 to 0.67), I^2 19%, p<0.00001 (4 RCTs, n=14,562)** High-income countries with chronic illness OR 0.93 (95% CI 0.73 to 1.19), I^2 10%, p=0.57 (6 RCTs, n=4,010) High-income countries OR 0.71 (95% CI 0.45 to 1.12), I^2 93%, p=0.14 (5 RCTs, n=27,886)	Pooled estimate of overall efficacy 28% (95% CI 7% to 44%) but much heterogeneity. **Vaccine efficacy in low-income countries 46% (95% CI 33% to 57%)**	Available evidence does not demonstrate that PPVs prevent all-cause pneumonia in adults due to substantial heterogeneity. **However, evidence of efficacy in otherwise healthy adults in low income countries.** Inconclusive efficacy for adults with chronic illness and high-income countries.

Definitive pneumococcal pneumonia					
Moberley et al (2013)(97) Systematic review and meta-analysis of 18 RCTs and 7 non-RCTs	Adults from low and high income countries with and without chronic disease Meta-analysis of data from 35,483 people from 10 RCTs comparing PPV to placebo.	Overall effect	Overall (RCTs): **OR 0.26 (95% CI 0.15 to 0.46), I^2 0%, p<0.00001 (10 RCTs, n=35,483**)	Protective efficacy 74% (95% CI 54% to 85%)	**Favours PPV**
Mortality					
Moberley et al (2013)(97) Systematic review and meta-analysis of 18 RCTs and 7 non-RCTs	Adults from low and high income countries with and without chronic disease Meta-analysis of data from 47,560 people from 14 RCTs comparing PPV to placebo.	Overall effect and subgroup analysis according to low/high income countries, and adults with chronic disease	Overall all-cause mortality (RCTs): OR 0.90 (95% CI 0.74 to 1.09), *I^2 69%*, p=0.3 (14 RCTs, n=47,560) **Subgroup analyses:** **Low-income countries** **OR 0.79 (95% CI 0.62 to 0.99), I^2 n/a, p=0.04 (1 RCTs, n=11,958)** High-income countries with chronic illness OR 1.13 (95% CI 0.90 to	No evidence of a protective effect overall	No evidence of protective effect overall but evidence of efficacy in healthy adults in low-income countries (NB. trials showing this were in settings where limited number of serotypes caused disease where pneumococcal disease was significant cause of mortality (mines).

			1.43), I^2 6%, p=0.29 (6 RCTs, n=3,603) High-income countries OR 0.88 (95% CI 0.67 to 1.17), I^2 79%, p=0.39 (7 RCTs, n=32,023) Mortality due to pneumonia: OR 0.71 (95% CI 0.44 to 1.16), I^2 72%, p=0.17 (9 studies, n=30,723) Mortality due to pneumococcal infection: OR 2.51 (95% CI 0.45 to 14.13), I^2 0%, p=0.3 (3 RCTs), n=2,445)		

C4 Summary of systematic reviews of the effectiveness of non-pharmaceutical interventions on reduction of the transmission of influenza

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size for ORs and RRs	Favours
Use of personal protective equipment					
Rainwater-Lovett et al 2014(12) Systematic review	Elderly residents, staff or both in LTCFs Meta-analysis of 37 observational studies reporting 60 outbreaks	Reduction in influenza like illness attack rates Comment: PPE considered glove and mask use, hand hygiene, and droplet precautions	Influenza A outbreaks: OR 0.53(95% CI 0.25 to 1.10) Influenza A or B outbreaks: OR 0.63 (95% CI 0.33 to 1.19)	Not significant Comment: Broad definitions of non-pharmaceutical interventions were used and rarely reported in detail	Consistent with a protective effect of PPE, but not statistically significant
Hand Hygiene					
Wong et al 2014(11)	People in the community Meta-analysis of 10 RCTs Comment: community setting defined as open setting without confinement and special care for the participants	Relative reduction in laboratory confirmed influenza and ILI: overall effect of hand hygiene with or without medical mask use with subgroup analyses for hygiene only, and hand hygiene combined with medical mask use	*Laboratory confirmed influenza:* Overall RR (hand hygiene +/- medical mask): 0.82 (95% CI 0.66 to 1.02), I^2 0%, p=0.07 (7 RCTs, n=8,902) Hand hygiene only: RR 0.90 (95% CI 0.67 to	18% non-significant reduction overall (hand hygiene with or without medical masks) on lab-confirmed influenza. Significant 27% reduction for hand hygiene plus medical mask group, compared with non-significant	**Hand hygiene plus medical masks**. Comment: Authors' quality of evidence (GRADE) – high for laboratory confirmed influenza outcome and moderate for ILI

			1.20), I^2 14%, p=0.47 (4 RCTs, n=6,035) **Hand hygiene plus medical mask:** **RR 0.73 (95% CI 0.53 to 0.99), I^2 0%, p=0.05 (5 RCTs, n=4,050)** *Influenza-like illness:* **Overall RR (hand hygiene +/- medical mask):** **RR 0.78 (95% CI 0.68 to 0.90), I^2 0%, p=0.0008 (8 RCTs, n=9,147)** Hand hygiene only: RR 0.86 (95% CI 0.71 to 1.04), I^2 0%, p=0.11 (5 RCTs, n=6,164) **Hand hygiene plus medical mask:** **RR 0.73 (95% CI 0.60 to 0.89), I^2 11%, p=0.002 (5 RCTs, n=4,166)**	reduction of 10% for hand hygiene only group for lab-confirmed influenza. Overall significant reduction in ILI of 22%. Significant reduction of 27% for hand hygiene plus medical mask group, compared with non-significant reduction of 14% for hand hygiene only group.	

Mask and respirator use					
Bin-Reza et al (2011)(13) Systematic review	People of all ages in community or health care setting	Laboratory-confirmed influenza or clinically diagnosed influenza and other respiratory infections	**RCTs:** 6 of 8 RCTs: no significant difference between control and intervention group (masks +/- hand hygiene). 1 household RCT: mask wearing plus hand-sanitizer reduced secondary transmission of URTI/ILI/Lab-confirmed influenza 1 cluster RCT (hospital based) found lower rates of clinical respiratory illness with non-fit-tested N95 respirators compared with medical masks. **Observational studies:** 8 of 9 studies: Mask and/or respirator independently associated with reduced risk of SARS.	-	No studies established a conclusive relationship between mask/respirator use and protection against influenza

			Comment: observational studies were for SARS not influenza so may not be generalizable to influenza		
Cowling et al (2010)(14) Systematic review	Volunteers, People in health care settings, people in community setting (outpatients, university dormitory residents) Narrative synthesis	N95 respirators and medical masks	n/a	*1 experimental volunteer study*: no influenza virus detected on Petri dish after coughing in people wearing mask or respirator compared with not wearing. *Health care settings*: *6 studies.* 1 study (RCT): no significant difference between N95 and medical masks 3 studies (1 RCT, 2 cross-sectional): no significant protective effect of mask use. 1 study (cross sectional): suboptimal use of standard precautions during high-risk procedures associated with increased risk 1 study (observational study in 'open-air' hospital in 1918: low case-fatality rate may be	**Limited evidence that masks may reduce infectiousness if worn by infected person.** Few data to support use of masks or respirators to prevent becoming infected.

				associated with use of natural ventilation and gauze medical masks. *Community setting: 4 RCTs:* No significant differences overall (but 1 study found significant difference between masks plus hand hygiene if implemented within 36 hours of illness onset in index)	

Smith et al (2016)(105) Systematic review	Health care workers wearing N95 respirators or medical masks Meta-analysis of 6 clinical studies (3 RCTs, 2 case-control studies, 1 cohort study). 23 surrogate exposure studies also included but not meta-analysed.	Comparison of respirators versus masks in preventing laboratory-confirmed respiratory infection, ILI, and workplace absenteeism	*Laboratory confirmed respiratory infection:* OR 0.89 (95% CI 0.64 to 1.24), $I^2$0% (3 RCTs, n=3,556) OR 0.43 (95% CI 0.03 to 6.41), I^2 n/a (1 cohort study, n=43) OR 0.91 (95% CI 0.25 to 3.36), I^2 0% (2 case-control studies, n=509) *Influenza-like illness:* OR 0.51 (95% CI 0.19 to 1.41), I^2 18% (3 RCTs, n=3,556) *Workplace absenteeism:* OR 0.92 (95% CI 0.57 to 1.50), I^2 n/a (1RCT, n=446)	No significant differences between respirators and masks	N95 respirators appeared to have a protective advantage over masks in laboratory setting, but insufficient data to definitively determine whether respirators superior to masks in clinical settings

Social distancing					
Rainwater-Lovett et al 2014(12) Systematic review	Elderly residents, staff or both in LTCFs Meta-analysis of 37 observational studies reporting 60 outbreaks	Reduction in influenza like illness attack rates	Influenza A outbreaks: OR 1.35 (95% CI 0.72 to 2.62) Influenza A or B outbreaks: OR 1.31 (95% CI 0.78 to 2.18)	Not significant Comment: Broad definitions of non-pharmaceutical interventions were used and rarely reported in detail	No effect

C5 Summary of Jefferson et al 2010(10) Cochrane systematic review 'Physical interventions to interrupt or reduce the spread of respiratory viruses' (not specific to influenza or to LTCFs)

Intervention	RCT (N=6)	Cluster-RCT (n=17)	Case control study (n=9)	Prospective cohort (n=16)	Retrospective cohort (n=6)	Before-after (n=13)
Frequent handwashing	-	3 trials in children effective	**OR 0.54 (95% CI 0.44 to 0.67),I^2 60%, p<0.00001** (7 studies, n=2,825)	2 studies – effect found 2 studies – no effect	-	1 study (military recruits) >5x per day effective
Handwashing with antiseptic	-	2 trials in children: antiseptic more effective than soap 1 trial in children: antiseptic = soap	-	2 studies: antiseptic added effect 1 study: no difference	-	-
Handwashing and surface disinfection	-	2 of 4 studies in children and families effective	-	-	-	1 school study effective
Hand disinfection	3 trials effective	-	-	-	-	-
Gargling with iodine	1 trial effective	-	-	-	-	-
Nose wash	-	-	**OR 0.30 (95% CI 0.16 to 0.57), I^2 0%, p=0.00023** (2 studies, n=1,225)	-	-	-
Virucidal tissues	-	1 trial small effect 2 trials no significant effect	-	1 study: effective	-	-

Disinfection of living quarters	-	-	**OR 0.30 (95% CI 0.23 to 0.39)** 1 study	-	-	-
Eye protection (mask/goggles)	-	-	**OR 0.10 (95% CI 0.05 to 0.17), $I^2$0%, p<0.00001** (3 studies, n=2,745)	-	-	-
Barriers (combined masks, gloves, gowns)	-	-	**OR 0.09 (95% CI 0.02 to 0.25), $I^2$0%, p=0.**00051 (2 studies, n=369)	1 study: gowns plus masks no added effect to handwashing	-	3 studies: effective when combined with isolation 1 study: gown and mask not effective added to isolation 1 study: gown and gloves effective in paeds ward

Mask	1 trial: medical masks no effect	1 trial: no effect if mask added to handwashing 1 trial: no effect of P2 mask 1 trial: mask added to handwashing effective if implemented within 36 hours after onset of illness 1 trial: mask added to handwashing effective during weeks 4 to 6 1 trial: no effect added to handwashing	**OR 0.32 (95% CI 0.26 to 0.39), I^2 44%, p<0.00001** (7 studies, n=3,216)	3 studies: masks effective	1 study: harm related to mask wearing	1 study: effective in children's hospital
N95 respirator	1 trial: medical masks non-inferior to N95 respirators	-	**OR 0.17 (95% CI 0.07 to 0.43), $I^2$39%, p=0.0002** (3 studies, n=817)	-	1 study: harm related to N95 wear	-
Gloves	-	-	**OR 0.32 (95% CI 0.23 to 0.45), I^2 42%** (6 studies n = 1,836)	-	1 study: harms related to gloves	-
Gowns	-	-	**OR 0.33 (95% CI 0.24 to 0.45), I^2 35%, p<0.00001** (5 studies, n= 1,460)	-	1 study: harms related to wearing gowns	1 study: no added effect in neonatal unit

Distancing	-	-	**-**	1 study: no effect (military recruits) 2 studies: cohorting effective in hospitals	1 study: cohorting effective in paediatric ward 1 study: cohorting effective with handwashing and gowns effective in military hospital	6 studies: isolation and early identification effective
Quarantine	-	-	**-**	1 study: isolation of close contacts effective	1 study: isolation of close contacts effective 1 study: non-significant marginal effect of border entry screening	-

C6 Summaries of systematic reviews evaluating the effectiveness of antivirals for treatment of influenza

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size for ORs and RRs	Favours
TREATMENT					
Reduction in time to alleviation of symptoms					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118) Systematic review and meta-analysis of published and unpublished studies	Previously healthy people with influenza	Reduction in mean time to first alleviation of symptoms compared with placebo	**Oseltamivir:** **16.8 hours (95% CI 8.4 to 25.1 hours), I^2 0%, p<0.0001 (8 study reports, n=3,954)** **Zanamivir:** **14.4 hours (95% CI 9.4 to 19.4 hours), I^2 9%, p<0.00001 (13 study reports, n=5,411)**	Oseltamivir: Small effect. 10% reduction from 7 days to 6.3 days Zanamivir: Small effect. 10% reduction from 6.6 days to 6.0 days	**Favours NAIs compared with placebo**

Dobson et al (2015)(109) Systematic review and meta-analysis of published and unpublished Roche sponsored placebo controlled RCTs	Previously healthy people with influenza	Reduction in median time to first alleviation of symptoms compared with placebo	**Oseltamivir:** **All patients (intention-to-treat population)** **17.8 hours (95% CI 9.3 to 27.1 hours), p<0.0001 (9 RCTs)** **Influenza infected patients population (intention-to-treat population)** **25.2 hours (95% CI 16.0 to 36.2 hours)**	Significant reduction in time to symptom alleviation in oseltamivir treated group compared with placebo: 15% for all patients, 21% for influenza infected	**Favours oseltamivir compared with placebo**
Dobson et al (2015)(109) Systematic review and meta-analysis of published and unpublished Roche sponsored placebo controlled RCTs	People aged ≥65 years	Reduction in median time to first alleviation of symptoms compared with placebo	17.4 hours (95% CI 49.8 hour reduction to 15.6 hour increase), n=596 (subgroup analyses in the intention to-treat infected population)	No significant reduction in time to alleviation of symptoms	No significant difference between oseltamivir treated and placebo in elderly people ≥65 years

Hsu et al(111) Systematic review and meta-analysis of observational studies	All populations with influenza or influenza-like illness	Reduction in duration of signs and symptoms (standardised mean difference)	**Oseltamivir:** **33 hour reduction (95% CI 21 to 45 hours), I^2 *89%,* p<0.00001 (6 studies, n=5,842** **Zanamivir:** **23 hour reduction (95% CI 17 to 28 hours), I^2 53%, p<0.00001 (3 studies, n=770)**	Significant reduction in duration pf symptoms and signs with oseltamivir and zanamivir	**Favours oseltamivir compared with no antiviral** Comment: Authors' quality of evidence (GRADE) – VERY LOW **Favours zanamivir compared with no antiviral treatment** Comment: Authors' quality of evidence (GRADE) – MODERATE

Burch et al (2009)(110) Systematic review and meta-analysis of published and unpublished RCTs (through company web sites, trial registers, and contact with manufacturers)	People presenting with symptoms of influenza (healthy adults and those in at-risk groups, including elderly either in mixed populations or as separate study population)	Reduction in median time to first alleviation of symptoms compared with placebo (Intention-to-treat population [ITT])	*Healthy Adults (ITT):* **Oseltamivir:** **13.3 hour reduction (95% CI 3.4 to 23.2 hours), I^2 0%, p=0.008 (4 RCTs, n=1,410)** **Zanamivir:** **0.57 day reduction (95% CI 3.4 to 23.2 days), I^2 38%, p=0.02 (6 RCTs, n=2,701)** *Elderly population:* Oseltamivir: 10 hours reduction (95% CI 45 hours fewer to 25 hours longer), I^2 n/a (1 trial only, n= RCTs, n=736) Zanamivir: 1.13 day reduction (95% CI 2.9 days fewer to 0.6 days more), I^2 0%, p=0.21 (5 RCTS, n=475)	Healthy adults: Significant reduction in time to symptom alleviation in oseltamivir and zanamivir treated group compared with placebo Elderly population: No significant difference between NAI groups and placebo groups	**Favours oseltamivir and zanamivir compared with no antiviral in healthy adults** Elderly people: No clear evidence of difference between oseltamivir nor zanamivir in the ITT elderly population

Hospitalization					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118) Systematic review and meta-analysis of published and unpublished RCTs	Previously healthy people with influenza that is not currently severe	Effect on hospitalization rates	Oseltamivir: RR 0.92 (95% CI 0.57 to 1.50), I^2 0%, p=0.73 (7 study reports, n=3,994) Outcome not reported for zanamivir trials	No significant effect	Oseltamivir no significant effect on hospitalization rates in previously healthy adults

Dobson et al (2015)(109) Systematic review and meta-analysis of published and unpublished Roche sponsored placebo controlled RCTs	Previously healthy people with influenza that is not currently severe	Effect on hospitalization rates	Oseltamivir: All patients (intention-to-treat population): RR 0.61 (95% CI 0.36 to 1.03), p=0.07 (8 studies, n=4,270) **Influenza infected patients population (intention-to-treat population):** **RR 0.37 (95% CI 0.17 to 0.81), p=0.013 (6 studies, n=2,374)**	No significant effect on hospitalization rates for all patients, although statistically significant effect in influenza-infected people	**Oseltamivir significantly reduces hospitalization in previously healthy adults infected with influenza, although numbers requiring admission are very small so interpret with caution**

Hsu et al(111) Systematic review and meta-analysis of observational studies	All populations with influenza or influenza-like illness	Hospitalization in oseltamivir treated patients compared with no antiviral	**Oseltamivir versus no antiviral: AdjOR: 0.75 (95% CI 0.66 to 0.89), I^2 0%, p<0.00001 (4 studies, n=150,710)**	Absolute effect of oseltamivir: 3 fewer hospitalizations per 1000 (1 to 4 fewer) compared with 12 hospitalizations per 1000 with no antiviral treatment	**Oseltamivir more effective than no treatment** Comment: Authors' quality of evidence (GRADE) – LOW
		Hospitalization in zanamivir treated patients compared with no antiviral	Zanamivir versus no antiviral: OR 0.66 (0.37 to 1.18), I^2 0%, p=0.16 (2 studies, n=4,761)	Absolute effect of zanamivir: 3 fewer hospitalizations per 1000 (6 fewer to 2 more) compared with 10 hospitalizations per 1000 with no antiviral treatment	No significant difference between zanamivir and no antiviral treatment Comment: Authors' quality of evidence (GRADE) – VERY LOW

Burch et al (2009)(110) Systematic review and meta-analysis of published and unpublished RCTs (through company web sites, trial registers, and contact with manufacturers)	People presenting with symptoms of influenza (healthy adults and those in at-risk groups)	Effect on hospitalization incidence in people treated with oseltamivir or zanamivir compared with no antiviral (Intention-to-treat population [ITT])	*Healthy adults (ITT):* Oseltamivir: OR 0.97 (95% CI 0.33 to 2.90), I^2 0%, p=0.96 (3 RCTs, n=2,071) Zanamivir: OR 1.37 (95% CI 0.86 to 2.17) (1 study in healthy young men only, n=588) *Elderly population:* Oseltamivir: ITT *infected* population (no ITT population data); OR 0.42 (95% CI 0.11 to 1.60) (1 study, n=477) Zanamivir: No data	No significant effect of oseltamivir or zanamivir treatment on incidence of hospitalization in healthy adults, nor elderly population	No significant effect of either oseltamivir or zanamivir (BUT very low number of events)

Lower respiratory tract complications					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118) Systematic review and meta-analysis of published and unpublished RCTs	Previously healthy people who develop severe influenza	Effect on self-reported, non-verified pneumonia (oseltamivir trials), or self-reported or radiologically confirmed pneumonia (zanamivir trials)	Oseltamivir: Overall RR 0.55 (95% CI 0.33 to 0.90), I^2 0%, p=0.02 (8 studies, n=4,452). **But** on subgroup analysis of 2 study reports (5 trials) that used detailed diagnostic data collection forms or reported on radiological confirmation of pneumonia (as opposed to collection of data onto non-specific adverse events or secondary/intercurrent illness form, the effect was non-significant (RR 0.69 (95% CI 0.33 to 1.44), I^2 0%, p=0.32) Zanamivir: RR 0.90 (95% CI 0.58 to 1.40), I^2 0%, p=0.65 (11 study reports, n=5,876)		Lack of credible evidence that NAIs reduce risk of pneumonia

Dobson et al (2015)(109) Systematic review and meta-analysis of published and unpublished Roche sponsored placebo controlled RCTs	Previously healthy people who develop severe influenza	Effect on pneumonia (including self-reported)	**Oseltamivir:** **All patients (intention-to-treat population):** **RR 0.56 (95% CI 0.42 to 0.75), p=<0.001 (9 studies, n=2,807)** **Influenza infected patients population (intention-to-treat population):** **RR 0.62 (95% CI 0.49 to 0.79), p=0.0001, 9 studies, n=4,202)**	Significant reduction in risk of pneumonia	**Oseltamivir more effective than no treatment** Comment: includes data cased on patient reported pneumonia and no distinction in trials between pneumonia caused by influenza and secondary bacterial pneumonia.

Hsu et al(111) Systematic review and meta-analysis of observational studies	All populations with influenza or influenza-like illness	Pneumonia in oseltamivir treated patients compared with no antiviral Respiratory complication in zanamivir treated patients compared with no antiviral	Oseltamivir: AdjOR: 0.83 (95% CI 0.59 to 1.16), I^2 *87%,* p<0.28 (3 studies, n=150,466) Zanamivir: OR 1.17 (95% CI 0.98 to 1.39), I^2 n/a, p=0.09 (1 study, n=4,674	Absolute effect of oseltamivir: 4 fewer pneumonias per 1000 (9 fewer to 3 more) compared with 21 pneumonias per 1000 with no antiviral treatment Absolute effect of oseltamivir: 17 more respiratory complications per 1000 (2 fewer to 37 more) compared with 113 respiratory complications per 1000 with no antiviral treatment	No significant effect of either oseltamivir or zanamivir Comment: Authors' quality of evidence (GRADE) – VERY LOW Pooled studies were very heterogeneous (I^2 = 87%)

Burch et al (2009)(110) Systematic review and meta-analysis of published and unpublished RCTs (through company web sites, trial registers, and contact with manufacturers)	People presenting with symptoms of influenza (healthy adults and those in at-risk groups)	Effect on pneumonia incidence in people treated with oseltamivir or zanamivir compared with no antiviral (intention to treat [ITT]	*Healthy adults (ITT):* Oseltamivir: OR 0.33 (95% CI 0.03 to 3.21), I^2 0%, p=0.34 (2 RCTs, n=789) Zanamivir: OR 1.36 (95% CI 0.63 to 2.93) (1 study in healthy young men only, n=588) *Elderly population (ITTI):* Oseltamivir: OR 0.95 (95% CI 0.29 to 3.15), 1 trial only, n=477 Zanamivir: OR 0.87 (95% CI 0.17 to 4.38), 1 study only, n=358	No significant effect of oseltamivir or zanamivir treatment on incidence of pneumonia in healthy adults	No significant effect of either oseltamivir or zanamivir (BUT very low number of events)

Mortality					
Muthuri et al (2014)(22) Meta-analysis of individual participant data	29,234 patients hospitalised with laboratory-confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 virus	Mortality risk in hospitalised patients treated with NAIs at any time compared to none. Adjusted OR (adjOR) after adjustment for steroids use, antibiotic use and treatment propensity score)	**All ages: adjOR 0.81 (95% CI 0.70 to 0.93), p=0.002** **Influenza confirmed: adjOR 0.82 (95% CI 0.70 to 0.95), p=0.01** **Adults: adjOR 0.75 (95% CI 0.64 to 0.87), p<0.001** NAIs started >48 hours after symptom onset: adjOR 1.20 (95% CI 0.93 to 1.54), p=0.15	Significant reduction in mortality in adults when NAIs started within 48 hours of onset	**Favours NAIs within 48 hours of symptom onset**

Hsu et al(111) Systematic review and meta-analysis of observational studies	All populations with influenza or influenza-like illness	Mortality in oseltamivir treated patients compared with no antiviral Mortality in oseltamivir treated patients compared with no antiviral	**Oseltamivir:** **AdjOR: 0.23 (95% CI 0.13 to 0.43), I^2 0%, p<0.00001 (3 studies, n=681)** Zanamivir: OR 0.47 (95% CI 0.02 to 8.97), I^2 n/a, n=87 (1 study, n=87)	Absolute effect of oseltamivir: 172 fewer deaths per 1000 (120 to 201 fewer) compared with 240 deaths per 1000 with no antiviral treatment Absolute effect of zanamivir: 35 fewer deaths per 1000 (66 fewer to 326 more) compared with 68 deaths per 1000 with no antiviral treatment	**Oseltamivir more effective than no antiviral treatment** Comment: Authors' quality of evidence (GRADE) – LOW No effect seen with zanamivir compared with no antiviral treatment Comment: Authors' quality of evidence (GRADE) – VERY LOW Very small study
Side effects					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118)	All trial subjects	Side effects	Oseltamivir: **Nausea RR 1.57 (95% CI 1.14 to 2.15)** **Vomiting RR 2.49 (95% CI**	Nausea: Number needed to harm (NNTH=28) Vomiting: NNTH =22	Oseltamivir: **Increased risk of nausea and vomiting.** Decreased risk of diarrhoea and general

Systematic review and meta-analysis of published and unpublished RCTs			**1.75 to 3.38)** Diarrhoea RR 0.67 (95% CI 0.25 to 0.97) General cardiac events RR 0.49 (95% CI 0.25 to 0.97) No significant increase in overall risk of psychiatric adverse events, although a dose-response effect reported in 2 trials. Zanamivir: Risk of reported adverse events RR 0.86 (95% CI 0.49 to 1.50) Nausea and vomiting RR 0.60 (95% CI 0.39 to 0.94) Diarrhoea RR 0.87 (95% CI 0.66 to 1.14)		cardiac events Zanamivir: Overall no significant increased risk of reported adverse events. Decreased risk of nausea and vomiting.

Dobson et al (2015)(109) Systematic review and meta-analysis of published and unpublished Roche sponsored placebo controlled RCTs	All trial subjects	Side effects	Oseltamivir: **Nausea RR 1.60 (95% CI 1.29 to 1.99)** **Vomiting RR 2.42 (95% CI 1.83 to 3.23)** Diarrhoea RR 0.75 (95% CI 0.6 to 0.95) Cardiac disorders RR 0.49 (95% CI 0.25 to 0.98) No significant effect on neurological or psychological disorders.		**Oseltamivir associated with increased risk of nausea and vomiting compared with placebo.** Decreased risk of diarrhoea and cardiac events

C7 Summary of systematic review of NAIs for prophylaxis against influenza

Ref	Population	Outcome, interventions	Results and statistical analysis	Effect size for ORs and RRs	Favours
PROPHYLAXIS					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118) Systematic review and meta-analysis of published and unpublished RCTs	All trial subjects (adults and children). A limited number of trials included elderly in LTCFs.	Reduction in symptomatic influenza people receiving prophylactic oseltamivir or zanamivir compared with placebo	**Oseltamivir:** ***In individuals:*** **RR 0.45 (95% CI 0.30 to 0.67), I^2 0%, p=0.00009 (3 study reports, n=2,479)** ***In households:*** **RR 0.20 (95% CI 0.09 to 0.44), I^2 n/a, p=0.00007 (1 trial only, n=405)** **Zanamivir:** ***In individuals:*** **RR 0.39 (95% CI 0.22 to 0.70), I^2 45%, p=0.0015 (4 trials, n=5,275)** ***Post-exposure prophylaxis in household or others with known contact with an index case*):** **RR 0.33 (955 CI 0.18 to 0.58), I^2 40%, p=0.00013 (5 trials,**	Number needed to treat benefit (NNTB) = 33 (26 to 55) NNTB = 7 (6 to 11) NNTB = 51 (40 to 103) NNTB = 7 (6 to 9)	**Prophylaxis with oseltamivir or zanamivir more effective than placebo at preventing symptomatic influenza in individuals and household contacts.**

			n=1,525)		
Okoli et al (2014)(24) Systematic review and meta-analysis of individual and household transmission studies (RCTs and observational studies)	Persons of any age of any age with laboratory confirmed influenza (seasonal, pandemic or avian), or with ILI, or those having had close contact with them.	Effect of oseltamivir, zanamivir or laninamivir (pre or post exposure) compared with no treatment, placebo or sham antiviral on community transmission (epidemiologically linked cases in setting *other than* hospitals, *care homes, nursing homes*, boarding schools, places of detention)	**Oseltamivir:** ***In individuals (laboratory-confirmed influenza):*** **OR 0.11 (95% CI 0.06 to 0.20), I^2 59%, p<0.001 (8 studies – RCTs and observational)** ***In households (laboratory confirmed influenza):*** **OR 0.23 (95% CI 0.09 to 0.59), I^2 39%, p<0.002 (2 studies)** **Zanamivir:** **In individuals *(laboratory confirmed influenza)*:** **OR 0.23 (95% CI 0.16 to 0.35), I^2 0%, p<0.001 (4 studies)** ***In households (laboratory confirmed influenza):*** **OR 0.18 (95% CI 0.10 to 0.31), I^2 0%, p<0.001 (2 studies)**	Both oseltamivir and zanamivir effective as prophylaxis for individuals and households irrespective of modality of use (pre or post exposure)	**Favours prophylaxis with oseltamivir or zanamivir compared with placebo or no antiviral prophylaxis.**
Jackson et al(119)	Children, adults and elderly receiving seasonal prophylaxis or post-exposure	Reduction in risk of developing symptomatic laboratory confirmed	*Oseltamivir (seasonal prophylaxis):* **Healthy adults:**	Oseltamivir effective in preventing laboratory confirmed influenza in seasonal prophylaxis in	Oseltamivir and zanamivir more effective than placebo or no prophylaxis in healthy adults, but

Systematic review	prophylaxis with oseltamivir, zanamivir or amantadine compared with those receiving placebo or no prophylaxis. (Included 3 studies of at-risk elderly subjects living in LTCF)	influenza	**RR 0.24 (95%CI 0.09 to 0.54)**(pooled estimate from 2 trials reported as single publication, n=1,039 **Frail elderly living in residential care receiving seasonal prophylaxis(113): RR 0.08 (95% CI 0.01 to 0.63) 1 trial, n=548** *Oseltamivir (post-exposure prophylaxis in households of mixed composition):* **RR 0.19 (95% CI 0.08 to 0.45), 2 trials, n=812** *Zanamivir (seasonal prophylaxis):* **Healthy adults: RR 0.32 (95% CI 0.17 to 0.63), 1 trial, n=1,107** Age ≥65 years: RR 0.20 (95% CI 0.02 to 1.72) [subgroup analysis of 1 trial in at-risk adults and adolescents, n=1896](114)	healthy adults and at-risk elderly and post-exposure prophylaxis in households. Zanamivir effective as seasonal prophylaxis in healthy adults and post-exposure prophylaxis in mixed households. Non-significant trend for protective effect of seasonal and post-exposure prophylaxis in at-risk elderly	evidence of their effectiveness in at-risk elderly is limited

			Zanamivir (post-exposure prophylaxis in households of mixed composition): **RR 0.21 (95% CI 0.13 to 0.33), 3 trials, n=2,416** Elderly in long-term care: RR 0.68 (95% CI 0.33 to 1.27), 1 study(25), n=494		

Side effects					
Jefferson et al (2014)(23), Jefferson et al (2014)(117), Heneghan et al (2014)(118) Systematic review and meta-analysis of published and unpublished RCTs	All trial subjects (adults and children). A limited number of trials included elderly in LTCFs.	Side effects	Oseltamivir: **Headaches RR 1.18 (95 CI 1.05 to 1.33), I^2 0%, p=0.005 (4 trials, n=3,434)** **Nausea RR 1.96 (95% CI 1.20 to 3.20), I^2 49%, p=0.007 (4 trials, n=3,434)** **Psychiatric events RR 1.80 (95% CI 1.05 to 3.08), I^2 0%, p=0.03 (4 trials, n=3,434)** Zanamivir: No significant increase in adverse events reported in zanamivir prophylaxis trials, including psychiatric and renal effects on-treatment		**Oseltamivir:** **Increased risk of headaches, nausea, and psychiatric events** Zanamivir: No increased risk of reported adverse events

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