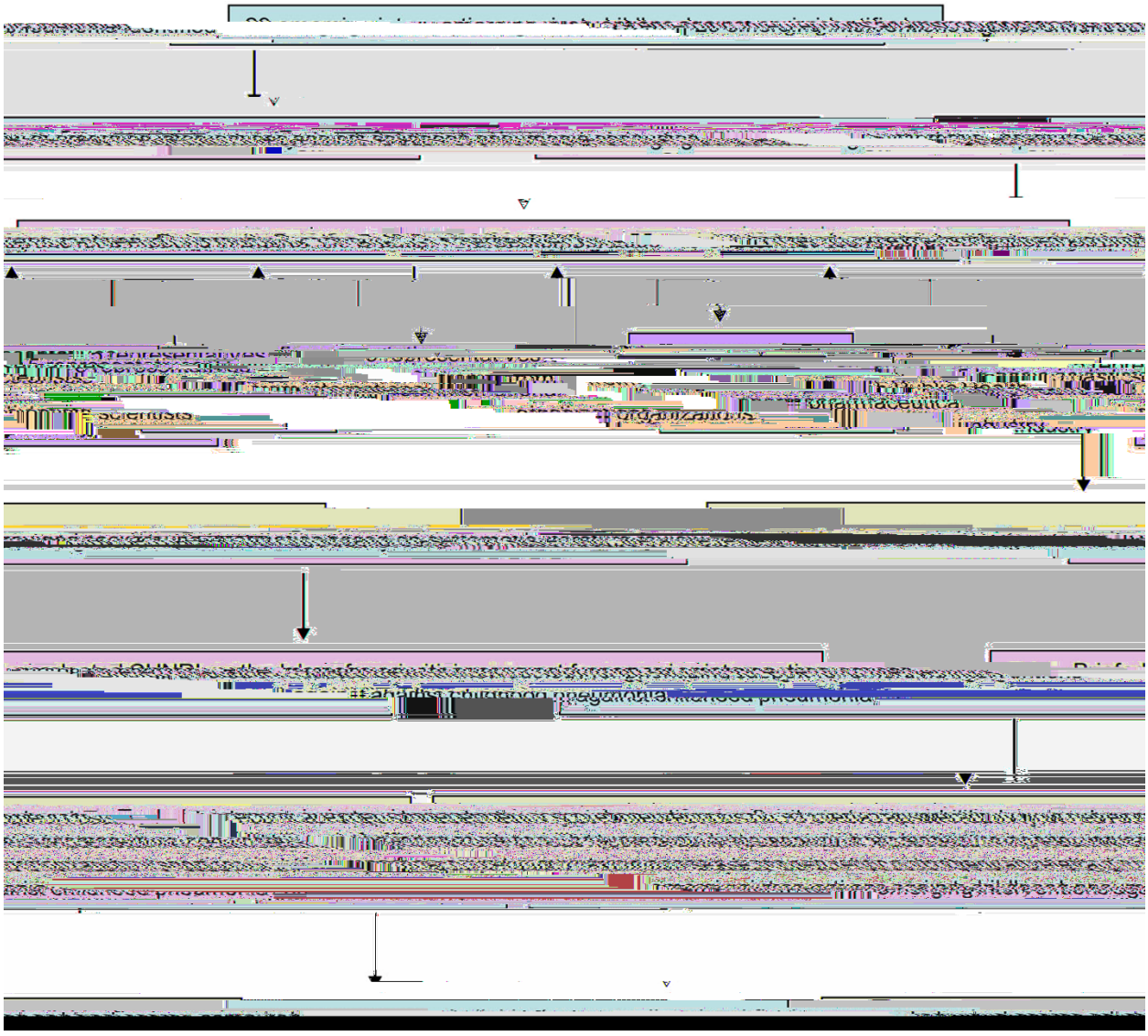
R s. - s

We identified 40 articles in June 2009 (updated to 80 articles and product monographs in May 2012) for inclusion. We have presented the updated review in this paper. Currently 101 different influenza vaccines are in various stages of development, of which 78 are yet to enter Phase III clinical trials [29].

Answerabilty - Is the science behind the research viable?

A - (EBIV)

Adjuvanted vaccines (Figure 3) have been shown to be antigen sparing and more immunogenic compared to non-adjuvanted vaccines, and may allow increased pro-



F . 2 A summary of Stage II of the CHNRI process of evaluation of an emerging intervention (an expert opinion exercise using the 9 CHNRI criteria) CHNRI- Child Health and Nutrition Research Initiative

C - (CCIV)

CCIV (Figure 4) have been demonstrated to be equally well tolerated and show potentially greater flexibility of supply during periods of high demand compared to EBIV [33-35]. Madin-Darby Canine Kidney (MDCK) cells and Vero cells have been researched extensively and candidate vaccines- Optaflu (Novartis) and Cevapan (Baxter) are well tolerated and have gained regulatory approval in the EU [36,37]. Newer vaccines have also shown great promise during clinical trials. Although CCIV addresses many of the current limitations faced by EBIV, their production capacity is largely dependent on individual virus strains as some replicate better than others in mammalian cells. This is also a relatively new technology and requires more sophisticated equipment such as a fermenter-based cell culture either using suspension cells or a micro-carrier-based culture [38].

L - (LAIV)

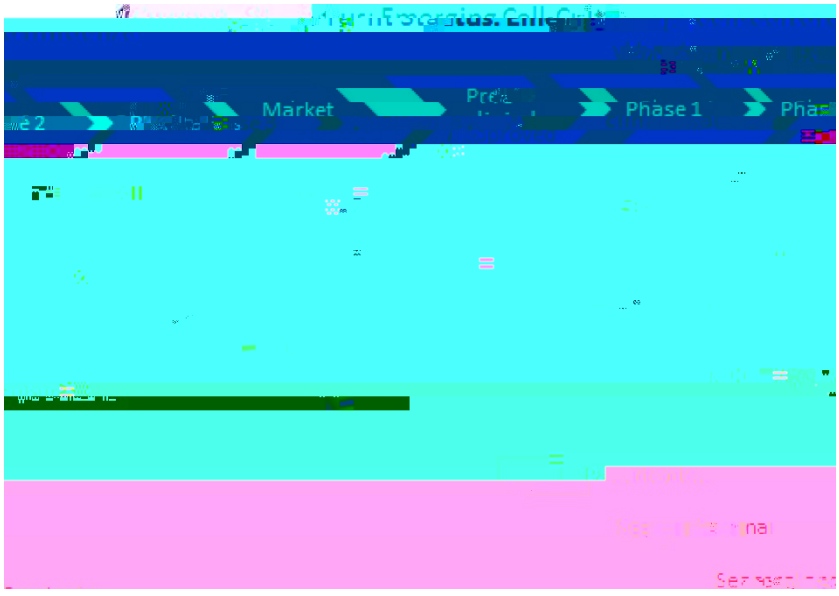
Current market-approved LAIVs are produced using the egg-based method (Figure 5) and therefore share the same advantages and limitations as EBIV. Drug companies are currently researching on developing LAIVs using cell-based technology. These have been shown to be safe and sufficient to produce a protective immune response in adult humans during Phase I and Phase II clinical trials and therefore might be an effective alternative to conventional EBIV [39-43].

F . 3 The current status of the research into emerging egg-based influenza vaccines WV- Inactivated Whole Virion

R (VLP)

In the case of recombinant vaccines, the answerability would depend on the type of virus-like particles (VLP) used. Similar to CCIVs, these vaccines can be rapidly produced in large quantities while avoiding the use of eggs. Animal studies show that they are able to induce satisfactory immune response that correlates to protection [44-49].

There are 19 companies currently developing different types of recombinant vaccines, indicating that there is great promise in the technology (Figure 6). Protein Sciences' insect cell vaccines have shown the most progress (currently in Phase II trials) and have demonstrated a degree of cross protection against both influenza A(H1N1) and A(H3N2) strains [50-55]. Vaccine manufacturers remain optimistic that recombinant vaccines shall be able to meet the demands during pandemics. However, further research is required to evaluate the answerability of this technology.



F . 4 The current status of the research into emerging cell-cultured influenza vaccines MDCK- Madin-Darby Canine Kidney cells

U /V ,- /DNA

Most of these vaccines are currently in pre-clinical and Phase I clinical trials (Figure 7, 8, 9). Therefore, more research is needed to evaluate the feasibility of these vaccines. Preliminary trials show that these vaccines are able to provide broad protective immunity across different influenza virus strains and are safe and well tolerated in animal and human studies [56-73].

Based on this evidence, the panel of experts expressed concern over the ability of emerging cross-protective

recent study, Johansson and colleagues demonstrated that viral co-infections increase the severity and duration of hospitalisation in patients with bacterial pneumonia [83]. For children aged below 2 years, although they reduce the risk for influenza by about a half, they are not significantly more efficacious than a placebo.

A -

On-going phase II and III clinical trials studying the immunogenicity of adjuvanted vaccines have reported higher immune response compared to the non-adjuvanted formulation [30].

C -

There are limited published data regarding the efficacy of newer CCIVs currently in development. Market approved CCIVs- Optaflu (Novartis) and Celvapan (Baxter) have both demonstrated adequate immunogenicity in large scale human studies and no serious adverse effects (SAEs) were reported [36,37]. They have both been approved by the European Medicines Agency (EMEA) in 2009. Both are undergoing phase III trials in the US. Bharat Biotech's HNVAC has been tested in one of the largest phase I, II, and III clinical trials in India and has

R (VLP)

VLP technology is relatively new and there are limited published data on their efficacy. Protein Science Corporation is developing seasonal (Flublok) and pandemic (Panblok) influenza vaccines which have shown favourable immunogenicity and tolerability during Phase I and II clinical trials [50,52,54]. Novavax's H1N1 VLP vaccine was well tolerated and immunogenic in a phase II clinical trial carried out in more than 4000 subjects in Mexico [55]. Medicago have also announced promising

demonstrated that viral co-infection increase the severity and duration of hospitalisation in patients with bacterial

taxes which makes predicting the cost of both existing and emerging vaccines complex.

Current deliverability of the trivalent vaccine is unable

capacity can be scaled up quickly when needed and the

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